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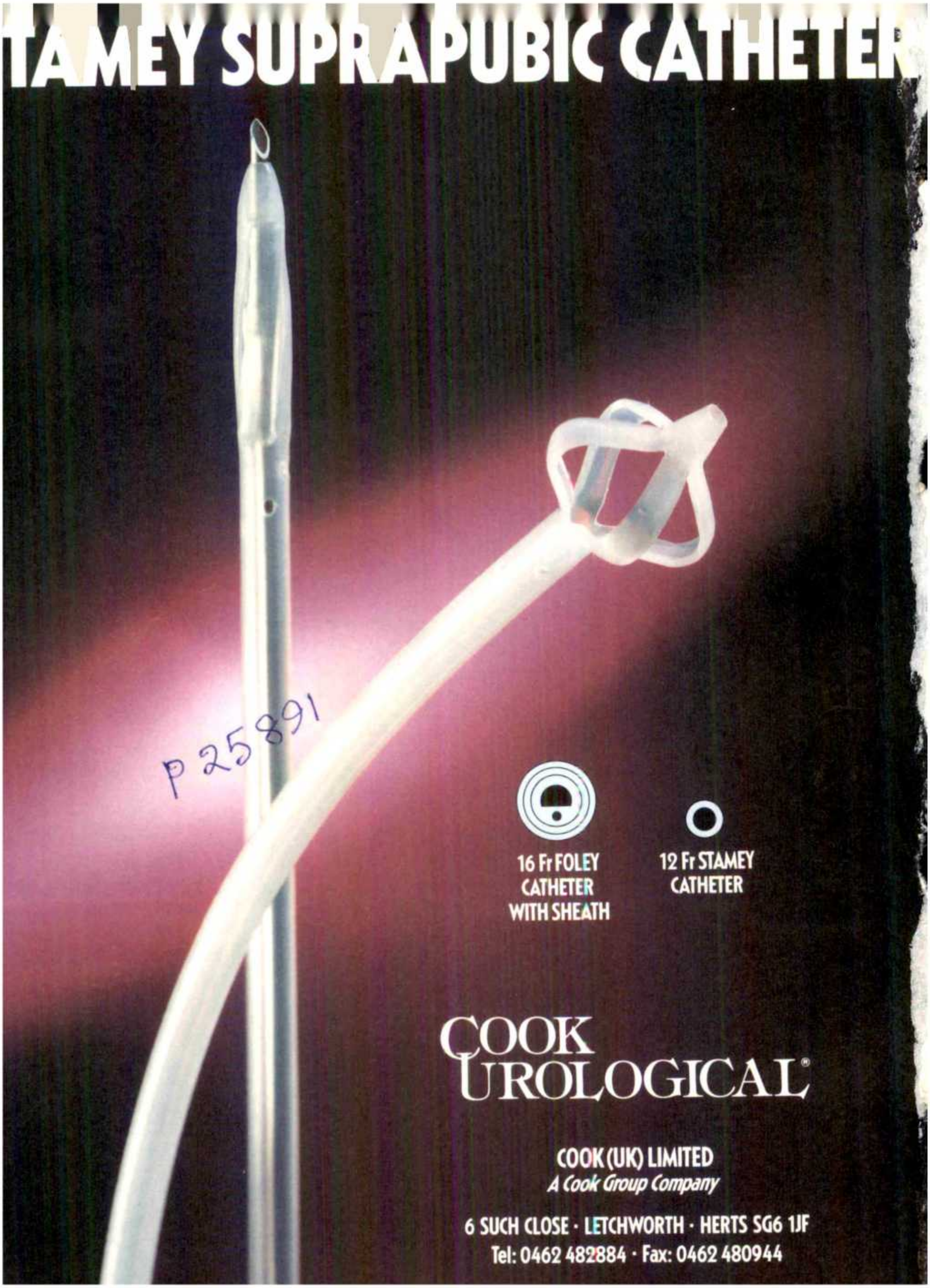

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REVIEW

Interactive Obstructive Uropathy in Man

D. A. JONES and N. J. R. GEORGE

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The entire urinary tract from glomerulus to external urethral meatus can be regarded as a single functional unit. The purpose of this unit is the formation and unidirectional excretion of urine at low pressure in order to maintain normal bodily homeostasis. Sometimes changes in one part of the system can be overcome by alterations elsewhere, but on other occasions this may result in inefficient or poor quality urinary excretion. Such a state of affairs, if allowed to persist for any length of time, can result in nephron failure and a uraemic death. Consequently it is imperative that urologists are conversant with interactions between upper and lower urinary tract and specifically what changes in lower tract function may cause deleterious effects on upper tract drainage.

Griffiths (1987) proposed, on the basis of theoretical models, that upper tract flow characteristics and pressures will vary according to the rate of urine production and the degree of bladder filling. These suggestions are supported by observations in pigs suggesting that detrusor instability in these animals influences upper tract pressures (Djurhuus and Constantinou, unpublished data) and that in high pressure porcine bladders vesical filling can affect vesicoureteric junction transport (Blok *et al.*, 1985).

Studies in man have also suggested a relationship between bladder and renal function. Lytton *et al.* (1967) described changes in urinary volume excretion related to bladder filling and proposed this to be due to a vesico-renal reflex, although subsequent attempts to clarify the nature of such a reflex have suggested that it may be a purely hydro-dynamic phenomenon (Soloway *et al.*, 1972). This latter view is supported by studies of IVU films in patients with full bladders or acute (painful) urinary retention which show rather "full"-looking ureters, suggesting some delay in upper tract drainage (Pierce and Braun, 1960; Gill and Curtis, 1977). In such circumstances, however, the duration of any upper tract dilatation is short-lived, limited by the suprapubic pain. Indeed, under these circumstances, release of endogenous neuropeptides, with known effects on smooth muscle, cannot be discounted as the cause of the appearances. Thus for further examination of the relationship between upper and lower urinary tract it is necessary to look at chronic, stable conditions which are more amenable to clinical and urodynamic study.

Non-neuropathic Bladder Dysfunction

Chronic urinary retention

The exact definition of chronic urinary retention is open to debate but in all of the subsequent studies it has been arbitrarily defined as the situation that exists when the volume of residual urine in the bladder after a normal void exceeds 300 ml.

Conventional urodynamic assessment. As long ago as 1955, Mitchell suggested that there might be different types of chronic retention with differing effects on upper tract function. This hypothesis was furthered by Abrams and George, who observed a relationship between upper tract dilatation and abnormally high bladder filling pressures during standard cystometry (Abrams *et al.*, 1978). However, these initial urodynamic studies were performed after the bladder had first been emptied by catheterisation. It soon became apparent that during subsequent cystometry it was impossible to refill the bladder to the original volume owing to the reduced compliance seen during rapid filling in patients with thick-walled, muscular, hypertrophied bladders (Coolsaet, 1985). Further studies

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were thus performed by slowly filling the bladder on top of the residual urine—attempting to imitate more closely the natural cycle of events—and subsequently in 1983 George *et al.* coined the term "high pressure chronic retention" (HPCR) to describe a group of patients with abnormally high intravesical pressures throughout the micturition cycle, thick-walled, trabeculated bladders and associated hydroureteronephrosis.

The salient urodynamic features of HPCR are firstly that after a normal void, *without any prior intervention*, a bladder pressure line can be inserted and will record a detrusor pressure greater than that within the abdominal cavity, *i.e.* a subtracted detrusor pressure greater than zero. This is the end void pressure below which bladder pressure never falls (unless drained by catheter) and is of fundamental importance in the pathophysiology of the associated upper tract obstructive uropathy (see below). Secondly, during medium fill cystometry, bladder pressures rise to abnormally high levels, suggesting reduced bladder compliance and resulting in a high end fill pressure (>15 cm of water above end void pressure). Finally, during voiding, high detrusor pressures (maximum voiding pressure >80 cm of water above end fill pressure) are associated with low flow rates confirming bladder outflow obstruction. Thus in HPCR, detrusor pressure is raised above normal throughout all phases of the micturition cycle.

In patients with chronic retention and low bladder pressures during filling neither those with a high (obstructed) nor a low (low pressure low flow states) voiding pressure have upper tract dilatation (George *et al.*, 1986) and therefore it would appear that it is persistently high pressures during the filling phase of the micturition cycle which are somehow related to the upper tract abnormality seen in HPCR. Further evidence supporting this hypothesis comes from Holden (personal communication), who compared 3 groups of patients: those with HPCR, *i.e.* reduced compliance during filling with obstructive voiding, those with phasic instability but normal compliance and obstructive voiding, and those with normal filling characteristics and obstructed voiding. Only patients with HPCR had upper tract dilatation. Styles *et al.* (1986b) confirmed that high end void and end fill pressures were associated with upper tract dilatation in chronic retention, although they suggested that the distinction between high and low pressure chronic retention was not absolutely clear-cut, with a few patients exhibiting normal upper tracts despite slightly raised bladder pressures. Whether such patients are at an early stage in the natural history of the disease process and are at high risk of future deterioration could only be determined from longitudinal studies.

Bladder pressures during natural filling in chronic urinary retention. Although standard urodynamics attempt to reproduce as nearly as possible what happens in the natural state, they inevitably represent a compromise because of the limited period of time available in which to perform the study. Machin *et al.* (1985) performed urodynamic studies during natural bladder filling in a heterogeneous group of patients with chronic retention and showed rather different characteristics from those described above. Marked phasic detrusor contractions were seen during natural bladder filling and end fill pressures were not as high as during standard cystometry. Similar changes have been reported by Styles *et al.* (1986a) using catheter tip pressure transducers for long-term ambulatory bladder pressure monitoring in patients with chronic retention. In those with upper tract dilatation their findings using standard cystometry were similar to those described by George *et al.* (1983). However, during long-term monitoring end void pressures, although elevated, were not as high as end void pressures recorded before standard cystometry, a finding which is difficult to explain as the natural end void status should be similar regardless of investigatory technique; it may well be that differences in the way the solid state tranducers are calibrated may account for some of these observed differences (James, 1990). During the natural filling recorded by ambulatory monitoring the slowly rising poor compliance curve of standard cystometry was replaced by recurrent phasic detrusor activity. The pressure rise during filling and end fill pressures were lower than during cystometry, although in some cases were still elevated above normal (>15 cm of water). A relationship between upper tract dilatation and various urodynamic parameters was sought but the best correlation was with the derived value "A_{20}". This is defined as the area under the pressure/volume curve for the 20 minutes' recording prior to a void and is a measure of the frequency, duration and amplitude of the phasic detrusor activity during this 20-minute period (Styles *et al.*, 1988).

Thus whatever the method of study, upper tract dilatation appears to be related to the duration and magnitude of bladder pressure elevation during filling: recurrent phasic detrusor activity during ambulatory monitoring is equivalent to poor compliance during standard cystometry. It is apparent that a detailed knowledge of the technique of lower tract investigation is crucial in order accurately to identify when the upper tracts are at risk.

Relationship between upper and lower tract dynamics in HPCR

Renography. Standard radioisotope renography in patients with HPCR prior to any intervention shows poor excretion of isotope while the bladder is full or with the patient supine. Assuming the erect posture or withdrawing a volume of urine equivalent to a normal void from the bladder results in rapid washout of tracer from the kidneys (George *et al.*, 1984). This suggests that the hydrostatic pressure (about 25 cm of water in the erect posture) between kidney and bladder and regular voiding are important factors which contribute to upper tract drainage into the bladder in HPCR. Indeed, prolonged periods of recumbency can result in deteriorating renal function (George *et al.*, 1984).

Combined renal pelvic and bladder pressure studies. Under conditions of normal hydration renal pelvic pressures in HPCR are always lower than simultaneously measured detrusor pressures and do not vary with bladder filling or even with the high intravesical pressures generated during voiding (Holden *et al.*, 1984).

When flow in the upper tract is increased by either oral fluid loading, administration of a diuretic or perfusion via a percutaneous nephrostomy (as in a Whitaker test), then renal pelvic pressures remain low, so long as the bladder is allowed to drain. Vesicoureteric junction transport can be visualised fluoroscopically at this time. If, however, the bladder is allowed to fill (as would happen in the natural state) while upper tract flow remains high, then the combination of this increased input and the increased vesicoureteric junction outflow resistance leads to a quite marked increase in renal pelvic pressures and vesicoureteric junction transport ceases owing to the induced functional obstruction (Jones *et al.*, 1988b). No reflux has been demonstrated to account for these changes.

It is thus apparent that the crucial factor contributing to upper tract problems in HPCR is the increased ureteric outflow resistance occasioned by bladder filling. Intravesical pressure becomes elevated to abnormally high levels only because patients with this condition are unable to sense their chronically distended bladder. It is the combination of bladder filling together with high urine flow rates which leads to potentially damaging high renal pelvic pressures. These may be kept at lower levels for longer periods by ensuring a uniform, moderate fluid intake and regular voiding pattern. Relief of bladder outflow obstruction and improvement in bladder emptying should provide satisfactory relief for the upper urinary tract (Jones *et al.*, 1991).

Renal parenchymal dysfunction in HPCR

The ultimate importance of upper and lower urinary tract interactive obstruction is that eventually the most proximal parts of the system, the nephrons, may become functionally impaired, with serious consequences for both glomerular and tubular function (Jones, 1987; Jones *et al.*, 1988a). Reduction in glomerular filtration leads to retention of urea and creatinine and eventually severe uraemia. Although tubular compensation for reduced glomerular filtration rate is relatively good, it is not perfect, and salt and water retention do occur. This is most commonly manifest by hypertension, which is seen in 50% of cases (Jones *et al.*, 1987a) and also by increased jugulovenous pressure, peripheral and pulmonary oedema. In some patients these features may be the presenting complaint and should always prompt a careful examination of the lower abdomen and an enquiry about urological symptoms. As in other patients with obstructive uropathy, hyperkalaemic acidosis may be present (Batlle *et al.*, 1981; Jones, 1987) and a defective urinary concentrating mechanism is widely recognised (Berlyne, 1961; Nilsson *et al.*, 1979; Jones, 1987).

Following relief of obstruction, in the absence of concurrent infection, some degree of renal functional improvement is the norm (Jones, 1987; Jones *et al.*, 1987b). This appears to occur in 2 phases—an initial tubular phase during which sodium and water balance is restored (thus blood pressure normalises and signs of congestive cardiac failure diminish) and plasma creatinine falls, and a secondary phase when glomerular filtration rate slowly recovers. Changes in the tubular phase of recovery are maximal during the first few days following relief of obstruction but may continue for up to 2 weeks. The second glomerular phase takes place between 2 weeks and 3 months (Jones, 1987; Jones *et al.*, 1988a).

Post-obstructive diuresis. It has been recognised for some time that following relief of bilateral ureteric obstruction (BUO) a post-obstructive diuresis (POD) and natriuresis may occur (Eiseman *et al.*, 1955; Vaughan and Gillenwater, 1973). Incomplete knowledge about HPCR and the nature of POD led to calls for slow bladder decompression in chronic retention to try and avoid fluid balance problems. In fact the shape of the bladder pressure/volume curve in HPCR dictates that a small reduction in volume leads to a large reduction in pressure and effective relief of obstruction (George *et al.*, 1984). Thus clamping of a catheter after draining 1 litre or other arbitrary volume is of no value. The key to safe management of POD lies in understanding the mechanisms involved.

An increase in salt and water excretion is universal following relief of BUO (Jones, 1987; Jones *et al.*, 1988a) but is not necessarily clinically apparent because it is often small and self-limiting. Three processes are thought to be important: excretion of retained salt and water, osmotic diuresis due to retained urea, and tubular dysfunction. The commonest mechanism is the first (Jones, 1987; Jones *et al.*, 1989) and this is usually of clinical benefit—blood pressure is normalised and signs of fluid retention reversed (Jones *et al.*, 1987a). Thus careful monitoring of the clinical state of hydration and extracellular fluid volume is vital. Daily body weight, 4-hourly erect and supine blood pressure and regular assessment of jugulo-venous pressure and other signs of congestive cardiac failure are necessary. The actual volume of urine excreted is monitored but is of secondary importance to the above signs. By careful attention to this routine it will be found that the majority of patients will self-regulate and stabilise with a significant decrease in plasma creatinine levels within 1 week, although minor fluctuations may continue for a little longer in more severe cases. Approximately 10% of patients will need intravenous supplements of normal saline (Bishop, 1985; Jones, 1987) for temporary "overshoot" hypovolaemia and only 1 to 2% will have serious prolonged problems of salt and water balance due to tubular dysfunction. It is these few patients in whom POD is life-threatening, but they can be identified as problem patients at an early stage by the assessment of extracellular fluid volume status as described and will usually have an initial urinary output in excess of 200 ml/h following relief of obstruction.

An important point in the management of these patients is that occasionally following relief of obstruction the distal tubule remains hyporesponsive to aldosterone which is physiologically suppressed during the obstructed state (Clarke *et al.*, 1991) and, paradoxically, plasma potassium can rise despite falling plasma creatinine levels and return of normovolaemia (Jones *et al.*, 1987b). This is a particular risk in patients previously treated with potassium-sparing diuretics or potassium supplements. Accordingly plasma potassium must be carefully monitored in the post-obstructive state.

Long-term functional recovery following surgery for HPCR and its relationship to bladder morphology. Following bladder outflow surgery for HPCR the majority of patients do well. By 6 months postoperatively upper tract dilatation has generally resolved or is much improved, residual urine is small and resting bladder pressures are low (Holden, personal communication). In a recent series from a single institution of 32 patients with a mean follow-up of 43 months, 16 showed definite renal functional improvement and 12 who had relatively well preserved initial function were stable. Only 4 showed signs of deterioration and in 3 of these another potential cause of deterioration was present. In only 1 patient was recurrent bladder outflow obstruction suspected (Jones *et al.*, 1991). This case, however, combined with a report (Sacks *et al.*, 1989) of 5 patients presenting over a 2-year period to 2 regional nephrology units requiring dialysis after previous bladder outflow surgery, suggests that long-term deterioration, whilst uncommon, may occur and regular follow-up is important, especially in younger patients.

Bladder outflow obstruction causes well recognised morphological changes in the detrusor consisting of increased smooth muscle cell size, increased collagen deposition within smooth muscle bundles and reduced cholinergic innervation density (Gilpin *et al.*, 1985; Gosling *et al.*, 1986). It has been postulated that the severity of these changes might allow prediction of the eventual functional outcome, but no correlation between the severity of these changes at the time of diagnosis and treatment and the eventual functional outcome has been identified (Jones *et al.*, 1991). Recent evidence suggests that following relief of obstruction reinnervation might occur (Cummings and Chisholm, unpublished material) and this may well account for the apparent disparity between the severe anatomical changes in the lower tract and the functional improvement seen in both lower and upper tract function.

Posterior urethral valve

The boy with bladder outflow obstruction due to posterior urethral valve resulting in a chronically distended, thick-walled bladder and secondary renal impairment is the paediatric equivalent of an elderly man with HPCR. There are, however, important differences between the two. In the valve patient the upper tract dilatation may be due to either reflux or obstruction and the problem is occurring at a critical time when renal growth should be taking place. There is thus more at stake in renal functional terms and less margin for error in the young boy compared with the elderly man. Nonetheless, the basic pathology is similar and it appears that high bladder pressures are the fundamental problem resulting in upper tract deterioration. Indeed it has been reported that patients with a pressure "pop-off" in the form of a bladder diverticulum, gross unilateral reflux with ipsilateral renal dysplasia or intra-uterine urinary extravasation usually have better initial plasma creatinine levels and a better long-term prognosis (Rittenberg *et al.*, 1988).

It is unfortunately well recognised that not all boys have a good outcome followng valve ablation either in terms of bladder function (Bauer *et al.*, 1979; Campaiola *et al.*, 1985; Peters *et al.*, 1990) or renal function (Campaiola *et al.*, 1985; Parkhouse *et al.*, 1988; Reinberg *et al.*, 1988). Some authorities report a better long-term functional outcome in patients who have undergone supravesical urinary diversion at the time of initial treatment (Krueger *et al.*, 1980; Casale, 1990), which suggests that there may be a vesical component contributing to the poor renal recovery in those not so treated. Similarly, graft survival following transplantation to a post-valve bladder is worse than that for patients transplanted for simple reflux nephropathy with no vesical problems (Reinberg *et al.*, 1988). A recent long-term follow-up of boys treated for posterior urethral valve identified 3 factors associated with eventual poor renal functional outcome: age less than 1 year at presentation, bilateral vesicoureteric reflux at diagnosis and lack of attainment of continence by the age of 5 years (Parkhouse *et al.*, 1988). Once again this association between lower tract dysfunction and renal dysfunction suggests that the bladder could be the cause of both problems.

Persistence of upper tract dilatation following valve ablation is not uncommon and evaluation of its significance when not due to reflux is particularly difficult. Indeed it was this problem that almost 20 years ago led Whitaker to explore the use of perfusion pressure flow studies (PPFS) to distinguish persistently obstructed from non-obstructed dilated systems. During these initial studies it was noted that bladder filling had an effect on the pressures measured in the renal pelvis during perfusion (Whitaker, 1973). These and subsequent PPFS have shown that following valve ablation, persistent upper tract obstruction may occur and is usually related to poor bladder compliance and incomplete emptying (Glassberg *et al.*, 1982a; Campaiola *et al.*, 1985; Peters *et al.*, 1990) such that the patient lives with a bladder pressure constantly elevated above normal. In these circumstances regular emptying by clean intermittent self-catheterisation has been shown to result in upper tract improvement (Campaiola *et al.*, 1985). Glassberg has classified upper tract PPFS following posterior urethral valve resection into type 1—non-obstructed with an empty and a full bladder; type 2—non-obstructed with an empty bladder but obstructed with a full bladder; type 3—obstructed with an empty and full bladder (Glassberg *et al.*, 1982b; Glassberg, 1985). The majority of problem patients are type 2 and these may be subdivided depending on whether the obstruction with bladder filling is related to low bladder pressures and physical distortion of the vesicoureteric junction or high bladder pressures due to poor vesical compliance (Mayo and Ansell, 1980; Glassberg, 1985). Most authorities feel that poor compliance is the main cause of problems and treatments ranging through anticholinergic drugs, double or triple micturition, clean intermittent self-catheterisation and augmentation cystoplasty have been recommended in order to achieve a good capacity low pressure bladder (Glassberg *et al.*, 1982a).

With regard to maintaining a low pressure reservoir, the importance of large 24-h urine volumes and residual urines is crucial. Patients with obstructive uropathy, even when stabilised, often have a defective urinary concentrating mechanism resulting in the passage of larger than average urine volumes. This is particularly pertinent, as in adults it appears to be high urinary flow rates in combination with bladder filling which cause high upper tract pressures to develop (Jones *et al.*, 1988b). In the presence of increased urine production, bladder filling is more rapid than normal and thereby deleterious high bladder storage pressures are achieved more quickly and for longer periods of time in each micturition cycle (Glassberg *et al.*, 1982b; Parkhouse and Woodhouse, 1990). For similar reasons a significant pseudo-residual (that volume of urine which drains into the bladder from the dilated upper tracts in the first few minutes following voiding) is of great importance. This can be adequately eliminated by double or even triple micturition to ensure that the whole urinary tract has been emptied, leaving the maximum period of time available for urine storage at low pressure (Glassberg *et al.*, 1982b).

Upper Tract Obstruction with Normal Bladder Function

From the preceding sections it will be appreciated that bladder pressures elevated above normal for prolonged periods of time are detrimental to upper tract drainage. However, this is in patients with abnormal bladders. Can such high pressures be attained in normal bladders for any length of time or is there a natural pressure escape valve when the patient senses a full bladder and voiding occurs?

In order to examine this further, Jones *et al.* (1990) studied 21 consecutive patients with unilateral hydronephrosis (5 of whom also had a hydroureter) but normal bladders who were referred for PPFS to clarify their upper tract urodynamic status. Of the 5 patients with hydroureteronephrosis, 1 was obstructed whilst perfusing with an empty bladder, 1 was non-obstructive with an empty and full bladder, and 3 were non-obstructive while perfusing with an empty bladder but converted to an obstructed pressure rise when the bladder was filled. Bladder filling pressures were normal in each case. In the 16 patients with pelvicaliceal dilatation alone a further small elevation in renal pelvic pressure was noted when perfusing with a full bladder in those with non-obstructed pressure rises but in no case was it sufficient to convert a non-obstructive study to an obstructive one. There were 2 interesting patients who, when upper tract perfusion was ongoing at the high flow rate of 20 ml/min, showed intermittent increases in renal pelvic pressure coinciding with subclinical phasic detrusor contractions during bladder filling. These patients had no lower tract symptoms other than a normal desire to void associated with the phasic activity. One of the patients had the loin pain for which he was being investigated reproduced at this point in the study.

With the presence of a hydroureter under diuretic conditions urine flow is through an "open tube" system and when outflow resistance (*i.e.* bladder pressure) is increased then there is equilibration of pressures across the vesicoureteric junction and renal pelvic pressure rises. This kind of flow may also occur in normal ureters at high flow rates (Griffiths, 1987) and may well be the explanation for the renal pelvic pressure changes seen in those patients with pelvicaliceal dilatation alone. It seems unlikely that this situation would occur in patients with classical pelviureteric junction obstruction because limited pelviureteric fluid transport would not allow high enough flow for open tube conditions to develop. The observations reported of renal pelvic pressure changes during bladder filling in patients with normal ureters may thus only apply if there is minor impedance to upper tract flow or it may even represent one end of the normal physiological spectrum.

From the foregoing discussion it is concluded that filling the bladder, whether it is normal or abnormal, does have an effect on upper tract urodynamics. It is suggested that in patients with hydronephrosis and either loin pain or deteriorating renal function in whom standard urodynamic studies are equivocal, the studies should be repeated during all stages of bladder filling under the stimulus of high flow rates in order to clarify upper tract drainage. The importance of 24-h urine volume and residual urine must also be considered when assessing the interaction between vesical and renal pelvic dynamics and their effects on renal function.

Neuropathic Bladder Dysfunction

Whatever the aetiology of the bladder dysfunction, the same principles that have been enumerated above will apply when assessing the interaction between upper and lower urinary tracts. Neuropathic bladder disorders are a well recognised cause of upper tract dysfunction, although this may take the form of either reflux or obstruction and certain urodynamic features are unique to these disorders.

The classification of neuropathic bladder dysfunction introduced by Rickwood *et al.* (1982) and supplemented by Mundy *et al.* (1985) is widely used in clinical practice. This classification, however, specifically relates to lower tract dysfunction—particularly continence—and not to upper tract changes. Mundy *et al.* (1982) did note that in 20 children with neuropathic bladder and vesicoureteric reflux, the reflux was not related to any specific urodynamic parameter, although 44% of 57 children (25 patients) with detrusor sphincter dyssynergia had an impaired glomerular filtration rate. Clinical experience suggests that most patients with upper tract obstruction (as opposed to reflux) fall into the so-called intermediate neuropathic group, that is patients with poor bladder compliance with superimposed phasic detrusor activity who have open bladder necks and fixed distal sphincter mechanisms resulting in the coexistence of varying degrees of distal sphincter obstruction and sphincter weakness incontinence. Thus patients "live" at a particular level on the compliance curve, leaking when detrusor pressure exceeds maximum urethral pressure but often not emptying efficiently. It is thought to be the abnormal pressures seen during bladder filling which account for upper tract problems in this group. This is supported by the observation that if the bladder outflow resistance is increased (*e.g.* by implanting an artificial urinary sphincter) in patients with low amplitude detrusor activity during filling, these may convert to intermediate type detrusor activity with associated upper tract deterioration (Murray *et al.*, 1988; Parry *et al.*, 1990).

A number of studies suggest a relationship between poor bladder compliance and upper tract dilatation (Ghoneim *et al.*, 1989; Hackler *et al.*, 1989; Weston *et al.*, 1989). There are, however, problems in attempting to quantify the problem. Normal levels of compliance are difficult to define because they vary according to the method of study, specifically with filling rate and time (Coolsaet, 1985), whether the bladder was emptied prior to study (*vide supra*) and changes in each individual investigation with the volume infused. Despite these problems in determining a reproducible value, one particularly poor prognostic factor would appear to be loss of compliance early in bladder filling (Ghoneim *et al.*, 1989; Weston *et al.*, 1989). Weston *et al.* (1989) reported 20 of 30 patients with this phenomenon having already suffered upper tract deterioration at the time of presentation. Critical bladder pressures were stated to be about 20 cm of water and patients showing early detrusor pressure rises to 40 cm of water had particularly rapid deterioration in renal function.

Natural fill ambulatory cystometry using catheter tip pressure transducers to monitor detrusor pressure for a mean of 3 voiding cycles over periods of 6 h have shown findings remarkably similar to those in HPCR (Webb *et al.*, 1989). Resting end void detrusor pressures are similar during ambulatory monitoring and standard fill cystometry and may be elevated above zero. During natural filling, regular phasic detrusor activity is seen to replace the poor compliance observed on standard cystometry. Akin to the situation in HPCR, the area under the pressure/volume curve for 20 min prior to voiding (Webb *et al.*, 1989) is statistically related to upper tract dilatation. In the same patients high residual urine volumes and poor compliance on conventional cystometry are also related to upper tract obstruction, *i.e.* the duration, frequency and amplitude or the total time bladder pressure remains above normal is what appears to be important in determining the effect on upper tract drainage.

Bladder outflow obstruction, usually detrusor sphincter dyssynergia or isolated distal sphincter obstruction, has also been associated with upper tract dilatation (McGuire *et al.*, 1981, 1983; Mundy *et al.*, 1982). Whether this is a risk *per se* or whether it reflects an ability of the detrusor to store greater volumes at higher pressures before leakage occurs is unclear. Maguire *et al.* (1981, 1983) reported upper tract deterioration when leak pressures exceeded 40 cm of water, although these patients also had poorly compliant detrusors. Churchill *et al.* (1990) suggested that bladder storage pressures above 35 cm of water were critical in regard to renal deterioration, whilst Stott *et al.* (unpublished material) showed that low compliance, outflow tract obstruction and detrusor pressure at capacity were all statistically associated with upper tract dilatation and that 80% of patients with detrusor pressures >30 cm of water at capacity had renal deterioration.

Thus bladder pressures between 20 and 40 cm of water have been shown to be deleterious to upper tract function and at a recent symposium on interactive obstruction the consensus was that detrusor pressures >25 cm of water for any length of time during an individual's micturition cycle are likely, when repeated over a period of time, to produce significant upper tract obstruction, and therapeutic efforts should be directed towards maintaining lower pressures wherever possible.

Clearly many patients will be on some form of treatment at the time of assessment (most commonly clean intermittent self-catheterisation) and studies must be tailored to represent that individual's current "physiological" status as nearly as possible in order to develop a clear representative picture of the problem under consideration. In this regard residual urine volumes, 24-h urinary volume output and frequency of bladder emptying (best assessed from a weekly urinary diary) are crucial pieces of evidence which, together with the urodynamic studies, will give an accurate representation of bladder pressures and the periods of time during which they appertain in the individual concerned.

In clinical practice it is apparent that many interrelated factors must be considered before an integrated approach to the patient with neuropathic vesicourethral dysfunction can be developed. In terms of upper tract deterioration, certain features carry bad prognostic significance and thus high risk groups can be identified which warrant particularly close surveillance; indeed a scoring system (Galloway *et al.*, 1991) has been proposed that takes account of the factors discussed. No patient with a score <50% maximum has developed upper tract deterioration after a 2-year follow-up, but it is too early and probably over-simplistic to rely too heavily on this at the present time. Finally, it must be remembered that urodynamic findings may change with time in patients with neuropathic dysfunction and ongoing urological supervision is essential to the proper management of such patients.

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Compensatory Hypertrophy Effectively Assesses the Degree of Impaired Renal Function in Unilateral Renal Disease

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Summary—A series of 66 children with unilateral renal disease and normal total renal function were reviewed with the aim of determining whether clinically detectable compensatory hypertrophy indicated severe contralateral renal impairment. The proportion of total renal function that was contributed by each kidney was determined using isotope renography (^{99m}Tc-DTPA for 46 children, ^{99m}Tc-DMSA for 20). Kidney length was measured from plain abdominal radiographs or intravenous urograms and hypertrophy was expressed as the renal size index (RSI). Of 37 kidneys with a RSI greater than 2 standard deviations from the mean, 36 had less than 15% of total function in the contralateral diseased kidney. Kidneys with less than 10 or 15% of total renal function could be selected with 97 or 80% sensitivity and 84 or 97% specificity, respectively, using the same RSI selection level.

The size of a kidney is proportional to its renal function, both in healthy and diseased kidneys, but the variable correlation between them has prevented this feature being of much clinical value (Aperia and Wikstad, 1977; Wilton and Aperia, 1980; Absy and Metreweli, 1987; El-Khatib and Kincaid-Smith, 1987). Previous studies have also shown that the size of a hypertrophied kidney is directly related to the degree of tissue loss in the contralateral kidney but again the individual predictive value is poor (Griffiths *et al.*, 1974; Miler and Mortensen, 1980; El-Khatib and Kincaid-Smith, 1987). Most studies on compensatory hypertrophy have been based on the effects of acute tissue loss such as occurs in nephrectomised patients (Aperia and Wikstad, 1977; Absy and Metreweli, 1987), living renal donors (Tapson *et al.*, 1985) or animal studies (MacKay *et al.*, 1932; Hayslett *et al.*, 1968). Chronic unilateral disease is more prevalent but fewer studies relating hypertrophy to remaining contralateral function have been carried out in this group of patients (Miler and Mortensen, 1980; Wilton and Aperia, 1980). Growth of the kidney begins soon after the contralateral acute injury but it takes 6–18 months to reach the final state of equilibrium (Aperia and Wikstad, 1977; Absy and Metreweli, 1987). In chronic disease functional and structural changes are concurrent with the contralateral deterioration but the eventual outcome is, however, similar to that of nephrectomy (Wilton and Aperia, 1980).

In the life of an individual the earlier the loss of renal tissue the greater the compensatory growth response. If autonephrectomy occurs *in utero* then the remaining kidney will reach almost double the expected size, although the hypertrophy does not begin until after birth (Laufer and Griscom, 1971; Absy and Metreweli, 1987). The degree of compensatory growth after nephrectomy decreases from 50% in children under 6 months to 10–15% in adults (MacKay *et al.*, 1932; Kaufman *et al.*, 1975; Taki *et al.* 1983; Tapson *et al.*, 1985), so that a study of the value of assessing renal hypertrophy should be more easily interpreted in children.

The aim of this study was to determine if the presence of compensatory hypertrophy effectively

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indicates poor function in the contralateral diseased kidney, in any one individual patient.

Patients and Methods

The clinical notes and radiographs of 66 children with unilateral renal disease were reviewed; 28 had pelviureteric junction (PUJ) obstruction, 29 had unilateral vesicoureteric reflux (VUR), 4 had xanthogranulomatous pyelonephritis, 4 had obstructing ureteroceles and one had neonatal renal vein thrombosis. Those with ureteroceles and 6 of those with VUR had unilateral duplex systems.

All children had normal serum urea and creatinine levels. Creatinine clearance was normal in the 12 children in whom it was measured and glomerular filtration rate was normal in another 35 children in whom it was estimated at the time of DTPA isotope renography. Glomerular filtration rate was estimated by using the Slope method, where 2 accurately timed blood samples are taken 120 and 240 min after injection of the isotope. This method is accurate if the percentage protein binding is below 3%, if all batches of isotope have the same degree of binding and the patient has normal hydration (Merrick, 1984). The requirement of this study was that the patients should have total renal function well within the normal range.

In the 46 ^{99m}Tc-DTPA studies, 6 sequential images were taken per minute for the first 5 min. Relative renal function was calculated from the total number of counts accumulated from each kidney in the period starting 60 s after arrival of activity in the kidney and ending 120 s later. In the 20 ^{99m}Tc-DMSA scintigrams, relative functioning renal tissue was calculated by comparing images of both kidneys taken 2 and 4 h after injection. Patients with obstructive disease who had had DTPA studies were chosen for this study only if their scans were done in the post-operative period (range 3 weeks–3 months) in order to minimise the effect of pooling on determining relative renal function. In all patients intravenous urograms (IVU) and isotope scans were performed within 2 weeks of each other.

The length of the hypertrophied kidney was measured along its longest axis from either a high quality plain abdominal radiograph or an IVU film. The distance from the upper border of the first to the lower border of the fourth lumbar vertebra was also measured from the same film in each case (Fig. 1). This measurement is called the L1–L4 vertebral length. The renal size index (RSI) was calculated for each child by dividing the kidney length by the L1–L4 vertebral length and multiplying by 100 (Miler and Mortensen, 1980).

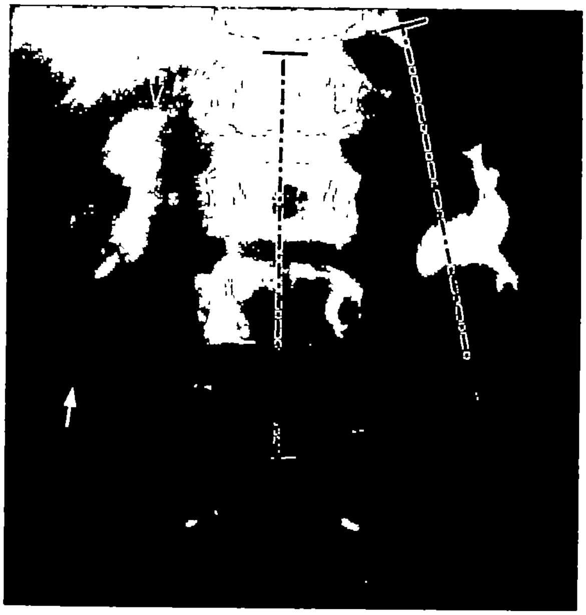

Fig. 1 Intravenous urogram of 11-year-old patient with unilateral reflux Dashed lines indicate the L1–L4 vertebral and kidney lengths. Arrows indicate the length of the diseased kidney.

$$\text{RSI} = \frac{\text{Kidney length} \times 100}{\text{L1–L4 Vertebral length}}$$

The kidney length and RSI of each patient were plotted on their respective nomograms (Hodson *et al.*, 1962; Miler and Mortensen, 1980). In Figure 2 the length of the hypertrophied kidney is plotted against the age of the patient. In Figure 3 the RSI is plotted against age.

Results

When kidney length alone was plotted against age (Fig. 2), 64 of 66 (97%) of all the hypertrophied kidney lengths were within the normal range for the population. There was no relationship between kidney length and the severity of the contralateral kidney damage, with many of those with lesser degrees of damage having kidney lengths further from the mean (Fig. 2).

In contrast, when the RSI values were plotted on the Miler and Mortensen (1980) RSI versus age nomogram (Fig. 3), the kidneys with the greatest degree of hypertrophy were matched to the most poorly functioning contralateral diseased kidneys: 98% (36 of 37) with RSI values above 2 SD of the population mean had less than 15% of the total

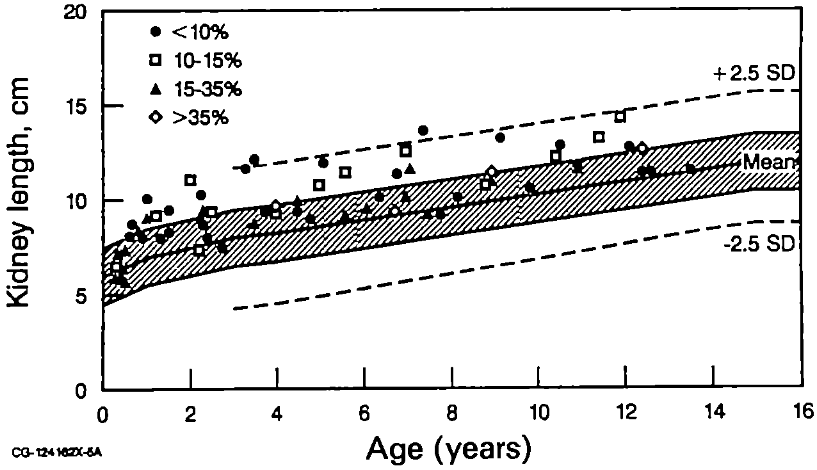

Fig. 2 Lengths of hypertrophied kidneys plotted for age on nomogram of Hodson *et al.* (1962). Each symbol indicates the percentage of total renal function in the diseased kidney. The shaded area is mean ±1 standard deviation of the normal population.

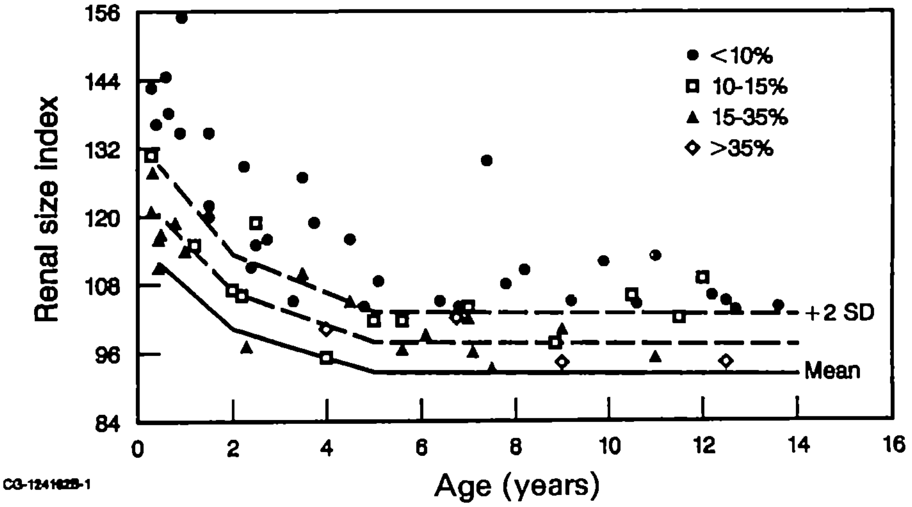

Fig. 3 Renal size index of the hypertrophied kidney plotted for age on nomogram of Miler and Mortensen (1980). Each symbol indicates the percentage of total renal function in the diseased kidney.

renal function in the diseased kidney. On the other hand, 70% (20 of 29) of those with RSI below the 2 SD level had more than 15% function in the diseased kidney. Of the 32 children with less than 10% of total renal function in the diseased kidney, 31 (97%) had an RSI greater than the 2 SD level. Conversely, 15 of 16 (94%) of those with 15–35% and all 4 with more than 35% function in the diseased kidney were below the 2 SD level. The patient demonstrated in Figure 1 had only 8% of total renal function in the diseased kidney and was placed well above the 2 SD level when using RSI but was placed just under the 1 SD level when plotted using kidney length alone.

If the RSI is used as a measure of hypertrophy 98% of children identified will have less than 15% of total renal function in the diseased kidney when using 2 SD as the selection level. Also, children with less than 10% of total renal function in their diseased kidney can be detected with 97% sensitivity, 84% specificity and 85.5% accuracy, while those with less than 15% on the impaired side will be detected with 80% sensitivity, 98% specificity and 81% accuracy if the same selection level is used.

Discussion

The degree of compensatory hypertrophy has been correlated to the amount of damage in the contralateral kidney in many studies on unilateral damage (Griffiths *et al.*, 1974; El-Khatib and Kincaid-Smith, 1987). While this gives significant results when examining groups of patients, the individual predictive value is poor because there is always a large intermingling of results from kidneys with different levels of renal function (Currarino, 1965; Griffiths *et al.*, 1974; Miler and Mortensen, 1980; El-Khatib and Kincaid-Smith, 1987). This study reaffirms that the use of kidney length alone, plotted on nomograms (Hodson *et al.*, 1962; Currarino, 1965; Tapson *et al.*, 1985) is not an accurate method of assessing compensatory renal hypertrophy or the amount of contralateral function.

Since kidney size is dependent on body size, the main flaw in the above method is that body size is not taken into account (Currarino, 1965). When considering kidney size, body height is the best estimator of body size and it is directly proportional to the L1–L4 vertebral height (Hodson *et al.*, 1962; Currarino, 1965). Griffiths *et al.* (1974) showed that kidney length is the best indirect measurement of kidney size. Both of these measurements are easily obtained from the IVU. The RSI thus incorporates both body and kidney size, which explains the improved accuracy in identifying the degree of renal damage.

Confirmation of the value of the RSI is dependent on the accuracy of the method of measuring relative function. Miler and Mortensen (1980) created the nomogram but could not prove the value of the RSI, since they used contrast excretion as an estimate of renal function, which is inaccurate (Hamby, 1969). Use of isotope renography in this study gives a much clearer picture of the close relationship between the degree of tissue damage and contralateral renal hypertrophy. Some of the DTPA scans still appeared to be affected by pooling even though only post-operative studies were used in patients with an obstructive disease. A closer relationship between compensatory hypertrophy and kidney damage would probably be noted if only DMSA scans were used, as it is an accurate method of calculating relative function (Merrick, 1984). Ureteric cannulation would allow direct measurement but is only applicable to an animal research study. As with other growth parameters in children, such as height and weight, separation of patients by sex should further improve the accuracy of the RSI.

The kidneys and vertebrae are both at the same distance from the X-ray plate. The RSI thus overcomes most of the magnification effects that occur in an IVU and allows comparison between films from different institutions, those done at different times, and even those in print.

The degree of compensatory hypertrophy is greater the younger the age at which damage occurs (MacKay *et al.*, 1932, Laufer and Griscom, 1971; Kaufman *et al.*, 1975; Tapson *et al.*, 1985), which means that children of the same age and having the same amount of renal injury will not have the same degree of hypertrophy if there is a difference between them in the time of occurrence of the injury. This accounts for some of the scatter of results seen in this study, as there was a trend, in the $<10\%$ unilateral function group, towards those with the highest RSI values being those patients with onset of the disease at an early age. Application of these findings to adults would be difficult because of the much smaller degree of change in kidney size after injury.

This study has shown that, in any individual child, compensatory hypertrophy is proportional to the amount of contralateral renal damage. It has also shown that 98% of hypertrophied kidneys with an RSI greater than 2 SD of the population mean will have less than 15% of total renal function in the contralateral diseased kidney. This fact could be of particular use in assessing children with PUJ obstruction as it is often difficult to get an accurate pre-operative determination of function on the affected side. Patients having 0–15% or 0–10% of total function in their diseased kidney can be identified with 80 or 97% sensitivity and 81 or 85.5% accuracy, respectively, using the same cut-off level.

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Selective Surgical Management of Renal Stab Wounds

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Summary—Patients with stab wounds and haematuria were selected for surgical exploration if they had signs of severe blood loss, an associated intra-abdominal laceration or major abnormality on the intravenous urogram (IVU). Patients without these signs were selected for non-operative management, consisting of bed rest, an intravenous antibiotic for 24 h and regular observation. Of 95 patients, 60 (63%) were selected for non-operative management (Group 1) and 35 (37%) were selected for primary surgical exploration (Group 2).

At surgery in Group 2, a major renal injury and/or associated intra-abdominal laceration was found in 31 patients. Thus a probably unnecessary operation was performed in only 4 patients (4% of the whole group of 95 patients). Renal complications occurred in 12 of the 60 patients (20%) in Group 1 and consisted mainly of secondary haemorrhage caused by an arteriovenous fistula (AVF) or pseudo-aneurysm. Management of the renal complications included segmental artery embolisation in 6, nephrectomy in 2, heminephrectomy in 1, open surgical ligation of an AVF in 1 and spontaneous resolution in 2 patients. The mean period of hospitalisation was significantly shorter in Group 1 (6.1 days) than in Group 2 patients (9.9 days).

Comparing the Group 1 patients who developed renal complications with those who did not, we would recommend more aggressive selection for surgery of those patients exhibiting clinical signs of shock, a fall in haemoglobin during observation, a palpable abdominal mass, a haemothorax and/or pneumothorax ipsilateral to the renal injury, and IVU signs of extravasation, non-function, delayed excretion or hydroureteronephrosis due to blood clots. An alternative management strategy would be to perform renal angiography before surgical exploration, with segmental artery embolisation as definitive treatment of the renal injury.

In the past decade, the policy of selective surgical management of low velocity penetrating abdominal injuries has become a widely accepted practice (Demetriades *et al.*, 1988; Meyer *et al.*, 1989). Although mandatory surgical exploration of penetrating renal injuries is still advocated by some, the selective approach has been extended to patients with stab wounds involving the kidney (Angorn, 1977; Bernath *et al.*, 1983; Heyns *et al.*, 1985). However, the selection criteria for non-operative management of renal stab wounds are not clearly defined and the results of selective management in large groups of patients have not been reported.

Patients and Methods

We reviewed the clinical records of 111 consecutive patients with stab wounds admitted for treatment in the Department of Urology, Tygerberg Hospital, between January 1984 and October 1990. Of these, 95 patients received primary treatment in this department and 16 were referred with complications after initial treatment elsewhere.

In the period under review, we followed a policy of selective surgical management of patients with stab wounds suspected of involving the urinary tract. After clinical assessment, a chest X-ray and a high dose intravenous urogram with tomograms were obtained if the patient was haemodynamically stable.

Patients were selected for primary surgical

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exploration only in the presence of one or more of the following: (1) signs of severe blood loss: systolic blood pressure <100 mmHg, haemoglobin <100 g/l, massive haematuria, a large flank mass, or a fall in haemoglobin despite blood transfusion; (2) signs of associated intra-abdominal injury: tenderness or guarding away from the wound, rigidity, rebound tenderness, absent bowel sounds; (3) major abnormality on the IVU: extrarenal extravasation of contrast medium, non-function of the entire or a major portion of the kidney.

The renal injury found at operation in patients selected for surgery was classified as minor (contusion, superficial cortical laceration) or major (laceration involving the pelvicaliceal system, major intrarenal vessels or renal pedicle).

Patients with none of the above indications for surgery were selected for non-operative management, consisting of bed rest, intravenous fluids, antibiotic cover for 24 h and frequent observation of the pulse rate, blood pressure, degree of haematuria, haemoglobin and abdominal signs.

Decisions on the management of individual patients were taken by the urological registrar and consultant on call, using the above selection criteria as guidelines. The patients in this review were treated by a total of 12 different urologists or trainees with widely varying levels of experience.

Statistical analysis was performed by Student's *t* test for parametric and Fisher's exact test for non-parametric data, and significance was accepted at $P < 0.05$. Values are expressed as mean ± standard deviation (SD).

Results

Of the 95 patients who received primary treatment in this department, 60 (63%) were selected for non-operative management (Group 1) and 35 (37%) were selected for primary surgical exploration (Group 2). Their characteristics are shown in Table 1 and the clinical and radiological signs at presentation are shown in Table 2. An IVU was not obtained in 3 patients (2 pregnant, 1 allergic) in Group 1 and in 4 patients in Group 2 who were haemodynamically unstable.

At operation in the 35 patients in Group 2, a minor renal injury was found in 6 (17%) and a major renal injury in 29 (83%). An associated intra-abdominal laceration was found in 12 patients (34%) and involved the colon in 4, liver in 3, diaphragm in 2, inferior vena cava in 2, and duodenum, ileum, spleen and mesentery in 1 patient each (more than 1 structure was involved in some patients). A minor renal injury without any associated intra-abdominal laceration was found in 4 patients (11%). Primary nephrectomy was performed in 11 (31%), heminephrectomy in 1 and suturing and drainage of the kidney in 23 patients (66%).

Table 1 Details of Patients

	Group 1 (n=60) (Non-operative) (%)	*Group 2 (n=35) (Surgical) (%)*
Age: Mean (years)	25.5 ± 8.4	28.4 ± 10.3*
Range	14–52	17–51
Sex: Male	50 (83)	29 (83)
Female	10 (17)	6 (17)
Lacerations: Number		
Mean	2.2 ± 1.7	2.0 ± 1.4
Range	1–7	1–6
Lacerations: Position		
Posterior	56 (93)	29 (83)
Anterior	2 (3)	1 (3)
Anterior and posterior	2 (3)	5 (15)
Abdomen	33 (55)	20 (57)
Thorax	18 (30)	7 (20)
Abdomen and thorax	9 (15)	8 (23)
Right side	21 (35)	14 (40)
Left side	33 (55)	17 (49)
Bilateral	6 (10)	4 (11)

*$P<0.05$ (Student's *t* test).

Table 2 Clinical and Radiological Signs at Presentation

	Group 1 (n=60) (Non-operative) (%)	*Group 2 (n=35) (Surgical) (%)*
Haematuria		
Macroscopic	41 (68)	24 (69)
Microscopic	19 (32)	8 (23)
Absent	0	1 (3)
Not known	0	2 (6)
Pulse rate >100/min	9 (15)	8 (23)
Systolic BP <100 mmHg	14 (23)	12 (34)
Hb<100 g/l	5 (8)	9 (26)*
Temperature >38°C	5 (8)	2 (6)
Shock	12 (20)	11 (31)
Abdominal examination		
Tenderness	40 (67)	30 (86)*
Guarding	24 (40)	20 (57)
Rigidity	4 (7)	7 (20)*
Mass	6 (10)	3 (9)
Rebound sign	6 (10)	16 (46)*
Bowel sounds absent	1 (2)	10 (29)*
Fall in haemoglobin	5 (9)	5 (20)
Chest X-ray		
Haemothorax	6 (10)	1 (3)
Pneumothorax	7 (12)	8 (23)
Haemothorax and pneumothorax	2 (3)	4 (11)
Intravenous urogram		
Not done	3 (5)	4 (11)
Normal	10 (17)	0*
Extravasation	11 (18)	17 (49)*
Non-function	5 (8)	10 (29)*
Filling defects	20 (33)	15 (43)
Delayed excretion	10 (17)	6 (17)
Perinephric haematoma	19 (32)	8 (23)
Intrarenal haematoma	5 (8)	3 (9)
Hydronephrosis	4 (7)	1 (3)
Hydroureteronephrosis	3 (5)	0

*$P<0.05$ (Fisher's exact test).

Complications occurred in 15 patients (25%) in Group 1 and in 15 (43%) in Group 2 (more than 1 complication was present in some patients) (Table 3). Renal complications occurred in 12 of the 60 patients (20%) managed non-operatively and consisted of secondary haemorrhage in 10, an arteriovenous fistula diagnosed at auscultation in 1, and a flank mass with persistent haematuria in 1 patient. The time between the stab injury and the development of secondary haemorrhage was 11.4 ± 12.1 days (range 4–36). Treatment of the renal complications consisted of selective arterial embolisation in 6 patients (3 AVFs and 3 pseudo-aneurysms), nephrectomy in 2, heminephrectomy in 1 and open surgical ligation of an AVF in 1; spontaneous resolution of haematuria occurred in 2 patients where angiography had demonstrated no vessel injury. The clinical and radiological findings at presentation in Group 1 patients, with and without later renal complications, are shown in Table 4.

Blood transfusion was required in 24 patients (40%) in Group 1 and in 31 patients (89%) in Group 2 ($P<0.05$, Fisher's exact test). The number of units of blood transfused was 3.5 ± 1.8 (range 2–9) in Group 1 and 4.7 ± 3.2 (range 2–14) in Group 2 ($P<0.05$, t test). The period of hospitalisation was 6.1 ± 5.3 days (range 1–23) in Group 1 and 9.9 ± 3.4 days (range 3–20) in Group 2 ($P<0.05$, t test). The period of hospitalisation in Group 1 patients with renal complications was 14.1 ± 5.0 days (range 2–23) and in Group 1 patients without renal complications it was 4.1 ± 3.0 days (range 1–19) ($P<0.05$, t test).

Follow-up was obtained in only 15 patients (25%) in Group 1 and 10 (29%) in Group 2. The mean period of follow-up was 44 days in Group 1 and 82

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Table 3 Complications

	Group 1 (n=60) (Non-operative) (%)	*Group 2 (n=35) (Surgical)*
Secondary haemorrhage	10 (17)	1*
Persistent haemorrhage	1	0
Bruit due to AVF	1	0
Wound sepsis	1	6*
Urinary tract infection	2	1
Acute tubular necrosis	0	1
Reno-cutaneous urinary fistula	1	1
Iatrogenic pneumothorax	0	4*
Respiratory infection	2	4
Secondary nephrectomy	1	1
Secondary heminephrectomy	1	0

* = $P<0.05$ (Fisher's exact test).

days in Group 2 patients ($P<0.05$, *t* test). Physical examination was normal in all patients, except for 1 in Group 1 with haemoglobin <100 g/l and 1 in Group 2 with systolic blood pressure >150 mmHg. A follow-up IVU was obtained in 5 patients in Group 1 (normal in 4, ureteritis cystica in 1) and in 3 patients in Group 2 (normal in 2, non-visualisation of a lower pole in 1).

In the period reviewed, 16 patients were referred to this department after initial treatment elsewhere (Group 3). The group included 13 men (81%) and the mean age was 27.3±8.3 years (range 17–42). None of these patients had an IVU within 3 days of being stabbed. The management before referral was non-operative in 13 and surgical (laparotomy) in 3. Of the 16 patients, 11 were referred with secondary haemorrhage, 3 with persistent macroscopic haematuria, 1 with signs of an acute abdomen and 1 with a flank mass and audible bruit. Renal arteriography was obtained in 9 patients. Selective embolisation of a traumatic pseudoaneurysm was performed in 6 patients, no vascular abnormality was seen in 2 and an AVF too large for embolisation was found in 1. Nephrectomy was performed in 4 patients. One patient had a laparotomy elsewhere, during which a retroperitoneal haematoma was left unopened. She was referred to us 3 days later in severe shock and died during reoperation and attempted suturing of a lacerated inferior vena cava. The amount of blood transfused in Group 3 patients (7.4±4.8 units, range 2–17) was significantly greater than in Groups 1 and 2, whereas the mean period of hospitalisation for Group 3 patients (10.8±8.4 days, range 1–36) was significantly longer than for patients in Group 1 but not Group 2 ($P<0.05$, *t* test).

Discussion

This study shows that in a large group of relatively young patients presenting with posterior stab wounds and haematuria a policy of selective management obviated surgical exploration in approximately 60%. An "unnecessary" operation (for a minor renal injury without any associated intra-abdominal laceration) was performed in only 4% of the 95 patients initially treated by us. Apart from avoiding unnecessary surgery and post-operative complications such as wound sepsis and respiratory embarrassment, the main advantage of selective non-operative management was that it significantly reduced the period of hospitalisation. These results in a larger group of patients confirm our previous recommendations on the selective surgical management of patients with stab wounds and haematuria (Heyns *et al.*, 1983, 1985).

The selection criteria which we have outlined are not separate, absolute indications for surgery, but guidelines which should be taken into account when deciding on the management of each individual patient. The findings at presentation which most often resulted in surgical exploration of our patients included haemoglobin <100 g/l, abdominal tenderness and rigidity, a rebound sign, the absence of bowel sounds, and extravasation and non-function on the IVU (Table 2). Nevertheless, in the patients selected for non-operative management, abdominal tenderness was present in almost 70% and clinical shock was present in 20%; haemoglobin <100 g/l, abdominal rigidity and a rebound sign were present in almost 10%, and on the IVU extravasation was noted in 18% and non-function in 8% (Table 2). This indicates that our

Table 4 Findings at Presentation in Group 1 Patients (Non-operative Management) with and without Renal Complications

	Renal complications	
	Present (n=12) *(%)*	*Absent (n=48)* *(%)*
Lacerations: Mean	3.3±1.8	2.0±1.6*
Range	1–6	1–7
Haematuria		
Macroscopic	9 (75)	32 (67)
Microscopic	3 (25)	16 (33)
Pulse rate >100/min	2 (17)	7 (15)
Systolic BP <100 mmHg	5 (42)	9 (19)
Haemoglobin <100 g/l	1 (8)	4 (8)
Clinical shock	5 (42)	7 (15)+
Fall in haemoglobin	2 (17)	3 (6)
Abdominal examination		
Tenderness	8 (67)	32 (67)
Guarding	7 (58)	17 (35)
Rigidity	0	4 (8)
Mass	2 (17)	4 (8)
Rebound sign	1 (8)	5 (10)
Bowel sounds absent	0	1 (2)
Chest X-ray		
Haemothorax and/or pneumothorax	6 (50)	9 (19)+
IVU		
Normal	0	10 (21)
Extravasation	4 (33)	7 (15)
Non-function	2 (17)	3 (6)
Filling defects (blood clots)	5 (42)	15 (31)
Delayed excretion	5 (42)	5 (10)+
Perinephric haematoma	3 (25)	16 (33)
Intrarenal haematoma	0	5 (10)
Hydronephrosis	1 (8)	3 (6)
Hydroureteronephrosis	2 (17)	1 (2)

*$P<0.05$ (Student's t test).
+$P<0.05$ (Fisher's exact test).

selection criteria were not used as separate, absolute indications for surgery, but that the patient's condition as a whole was considered.

The diagnostic value of an IVU in penetrating renal injury has been questioned (Carroll and McAninch, 1985; Federle *et al.*, 1987) and contrast-enhanced computed tomography (CT) is being promoted as the primary diagnostic study in this situation (Phillips *et al.*, 1986; Hauser *et al.*, 1987; Meyer *et al.*, 1989). Nevertheless, the expense and limited availability of CT mean that an IVU with nephrotomography remains the best primary imaging modality in patients with suspected renal injury (Carroll and McAninch, 1989; Peterson, 1989).

Extravasation of contrast or non-function on the IVU are generally accepted as indicative of major renal injury (Bergren *et al.*, 1987; Carroll and McAninch, 1989). Although extravasation alone is not regarded as an absolute indication for surgical exploration of the kidney (Bernath *et al.*, 1983; McAninch and Carroll, 1989), patients with extravasation and non-visualisation on the IVU who are treated conservatively are at risk of developing renal complications (Wilson and Ziegler, 1987). It has been stated that if one relies solely on the IVU, abnormal but non-specific findings (such as poor opacification or caliceal distortion) are an indication for surgical exploration (Carroll and McAninch, 1985, 1989), unless renal angiography or computed tomography is performed to delineate the extent of the injury more clearly (Leppaniemi *et al.*, 1989).

One of the worrying aspects of the present study is the high rate of renal complications (20%) in the patients selected for non-operative management. The incidence of secondary haemorrhage after non-operative management in 2 other series of patients with penetrating renal injury was 18% and 19% (Angorn, 1977; Bernath *et al.*, 1983). One study has reported an incidence of delayed bleeding of only 3% after renal exploration for blunt or penetrating trauma (McAninch and Carroll, 1989). In our previous studies of immediate surgical exploration of renal stab wounds, the incidence of delayed renal bleeding was 10 to 15% (Heyns *et al.*, 1983, 1985). The incidence of this complication may be related as much to the primary nephrectomy rate as to the skill or experience of the surgeon undertaking repair of the injured kidney.

Renal angiography and segmental artery embolisation can successfully control secondary renal haemorrhage in 80 to 100% of cases, with a low complication rate (Uflacker *et al.*, 1984; Hemingway and Allison, 1988; Fisher *et al.*, 1989; Kantor *et al.*, 1989). However, in the present study the mean period of hospitalisation in patients who required renal angiography and embolisation after non-operative management was 14 days, compared with only 4 days for those without renal complications and 10 days in those selected for primary surgery. Secondary haemorrhage after non-operative management thus defeats the objective of reducing bed occupancy by a policy of selective management.

Comparing the patients in this study who developed renal complications during non-operative management with those who did not, the following appeared to be slightly (although not always significantly) more common: systolic blood pressure <100 mmHg, clinical signs of shock, a fall in the haemoglobin level, an abdominal mass and guarding, a haemothorax and/or pneumothorax, and some abnormality on the IVU, including extravasation, non-function, delayed excretion and hydroureteronephrosis due to blood clot obstructing the ureter (Table 4). This indicates that we should perhaps be more aggressive in selecting for surgery those patients exhibiting some of these signs. An alternative management strategy would be to perform renal angiography before any surgical exploration of such patients, with segmental artery embolisation as definitive treatment of the renal injury (Uflacker *et al.*, 1984; Fisher *et al.*, 1989).

The findings in patients referred to us with complications after initial treatment elsewhere illustrate 2 important points: (1) non-operative management should never be undertaken without first obtaining, at the very least, an IVU of sufficient quality; (2) during laparotomy for bowel lacerations caused by penetrating injury a retroperitoneal haematoma should be opened and adequately explored, unless the surgeon is inexperienced, in which case the patient should be referred immediately for re-evaluation by an experienced surgeon.

A potential hazard of the non-operative management of stab wounds is the risk of an unrecognised diaphragmatic laceration. The roentgenographic findings, even those provided by CT, are often non-specific (Feliciano *et al.*, 1988; Fletcher *et al.*, 1989; Madden *et al.*, 1989). The mortality rate in patients with transdiaphragmatic bowel herniation after a previous stab wound can be as high as 36% (Madden *et al.*, 1989). Although it has been questioned whether diaphragmatic stab wounds can heal spontaneously, the incidence of delayed diagnosis of penetrating diaphragmatic injuries in patients with stab wounds is certainly very low (Demetriades *et al.*, 1988; Feliciano *et al.*, 1988). Delayed diaphragmatic bowel herniation after a previous stab wound occurs predominantly on the left, since the bulk of the liver prevents herniation through defects on the right (Feliciano *et al.*, 1988; Madden *et al.*, 1989). It has been suggestd that all patients with stab wounds that penetrate the lower left side of the chest (for example, those with a haemothorax or pneumothorax and ipsilateral kidney laceration) require laparotomy, if only to repair the diaphragmatic injury (Madden *et al.*, 1989).

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Pulsed Dye Laser Lithotripsy—the Toa Payoh Hospital Experience

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Summary—We report our experience with pulsed dye laser lithotripsy in the treatment of 100 ureteric stones in 95 patients over a 14-month period from July 1989 to September 1990.

The overall rate of successful stone fragmentation was 97%. There was a low incidence of minor complications—mild haematuria, ureteric colic and urinary tract infection; ureteric perforation occurred in only 3 patients, all of whom were successfully treated conservatively.

Pulsed dye laser lithotripsy is a safe and effective mode of treatment for ureteric stones. Current indications for laser fragmentation of stones are ureteric stones, impacted pelviureteric junction stones and Steinstrasse.

The last 2 decades have seen many advances in the treatment of ureteric stone disease. The advent of percutaneous procedures in the 1970s and improvements in endoscopic methods have reduced the need for open surgery for ureteric stones. Furthermore, the development of extracorporeal shock wave lithotripsy (ESWL) in the early 1980s provided another useful therapeutic option. Stone fragmentation by the pulsed dye laser is a fairly new mode introduced in the last few years. Laser energy delivered to the stone creates a plasma on its surface which results in an acoustic wave shattering the stone. The recent development of small calibre ureteroscopes has enhanced the efficacy and safety of laser fragmentation of stones at all levels of the ureter.

Patients and Methods

A retrospective analysis was performed on 95 patients with 100 ureteric stones.

The indications for surgery were pain, haematuria or obstruction of the urinary tract.

In all patients the diagnosis of ureteric calculi was confirmed on intravenous urography. Only endoscopically visualised stones were included in the study. The size of the stone was measured from the X-rays and radiolucent stones were assessed at endoscopy. The stones were classified according to their radiographic and endoscopic appearance since we do not have the facility for stone analysis. For example, calcium monohydrate oxalate stones would be radiodense and pigmented black or dark brown with a smooth surface. On the other hand, dihydrate stones have a yellow spiculated coralline appearance and would be less radiodense; in addition, these stones are fragmented easily during lithotripsy. Radiolucent stones were grouped into a separate category. The site of the stone in the ureter was assessed initially from the X-rays and confirmed at endoscopy.

The Technomed Pulsolith laser lithotriptor was used; it is a second generation lithotriptor capable of generating a higher level of laser energy and, therefore, a higher rate of successful stone fragmentation. At the operating wavelength of 504 nm, the laser energy is maximally absorbed by most stones and minimally by tissue. A 320 μm fibre was used to deliver 135 mJ of energy. Ureteric access was achieved retrogradely by means of a 7.2 F semirigid mini-ureteroscope. It is capable of 5 cm of passive flexure at its tip and its semirigid construction allows for easy manoeuvrability and good access to all levels of the ureter. The small diameter of the mini-ureteroscope obviates the need for dilatation of the ureteric orifice, thereby avoiding the risk of

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ureteric reflux and reducing the incidence of traumatic strictures. The mini-ureteroscope is excellent for impacted tunnel calculi and could be used with topical anaesthesia for distal stones in females.

A plain abdominal radiograph was done for all patients in the post-operative and follow-up periods; intravenous urography was performed in selected patients. Success of laser ureterolithotripsy was defined as complete stone fragmentation and a stone-free state on follow-up. Patients were discharged from further follow-up only when they were stone-free.

Results

There were 95 patients, of whom 66 were male and 29 were female. The average age was 45 years. The distribution by age groups is shown in Figure 1.

The most common presenting symptom was ureteric colic followed by haematuria. The remainder presented with urinary tract infection and a few were asymptomatic (Fig. 2).

The majority of the stones were found in the lower ureter (55), with the remainder evenly distributed in the upper (22) and mid (23) ureters (Fig. 3). The most commly encountered stone was of dihydrate composition, followed by monohydrate stones, and the remainder comprised mainly uric acid stones (Fig. 3). Stone diameter ranged from 5 to 25 mm, average 9.1 mm (Fig. 4).

In the majority of patients the operating time was 30 min or less. Several patients required a longer duration because of difficulty in gaining ureteric access, which was due to the tangential situation of the ureteric orifices, "high" bladder necks and enlarged prostates. Distorted ureteric anatomy from previous surgery was responsible in a few cases. A number of cases in the early stages of the study were due to the "learning curve" in the use of the semirigid mini-ureteroscope. Increased stone burden and hardness that necessitated a longer application of the laser to achieve fragmentation accounted for the remaining cases (Table 1).

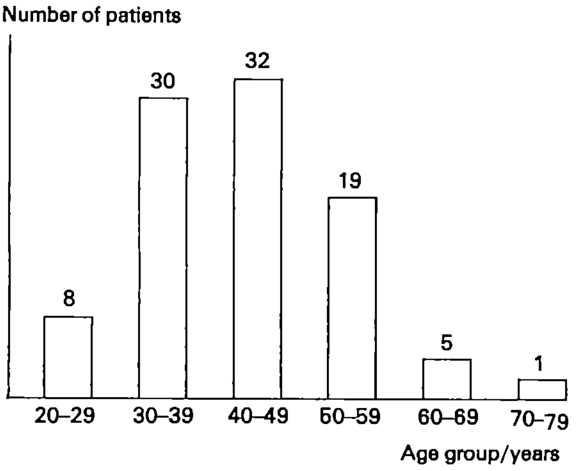

Fig. 1 Distribution of patients' ages.

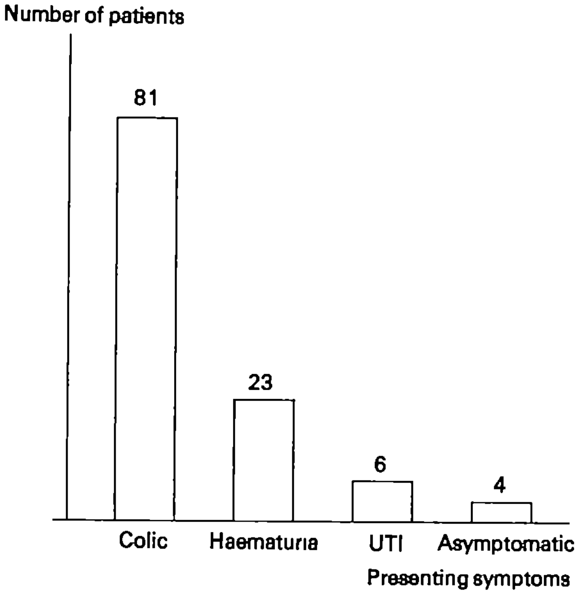

Fig. 2 Frequency of presenting symptoms.

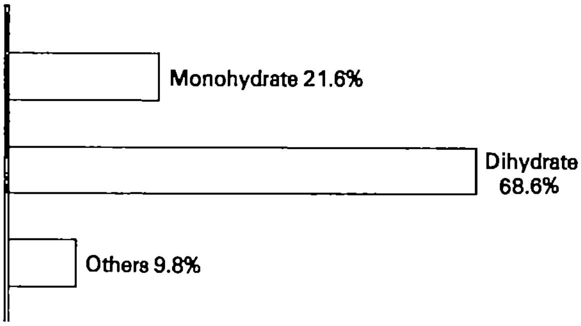

Fig. 3 Percentage of stones by composition.

Regional anaesthesia was used in 75 patients, with general anaesthesia in the remainder.

The average duration of hospitalisation was 4 days. In 6 selected patients, laser lithotripsy was performed on a day-surgery basis (Table 2). A total of 20 patients were hospitalised for 6 or more days; 7 of these patients required a repeat procedure on a subsequent occasion during the same period of

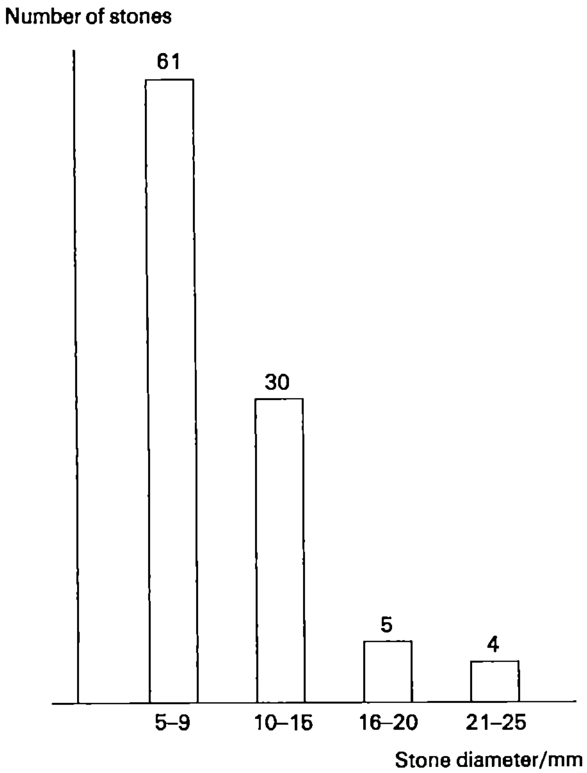

Fig. 4 Distribution of stones by size.

hospitalisation. Ten patients had a longer hospital stay because of complications following endoscopy and the remaining 3 underwent open surgery, which necessitated a longer period for post-operative recovery.

The average period of follow-up was 2.5 months and patients were discharged from follow-up only when they were stone-free. Three patients did not attend for follow-up (Table 3).

Of 100 ureteric stones, 90 successfully fragmented after a single procedure. Seven stones required repeat laser lithotripsy, which was successful in all cases. Thus the overall rate of successful stone fragmentation was 97%. Open surgery was performed on 3 patients with complete failure of fragmentation. All 3 stones were of monohydrate composition.

Table 1 Distribution of Patients by Operating Time

Duration of operation (min)	*No. of patients*
1–30	57
31–60	27
61–90	5
91–120	6

Table 2 Distribution of Patients According to Hospitalisation

Duration of hospitalisation (days)	*No. of patients*
Day surgery	6
1–5	71
6–10	10
11–15	5
16–20	5

Table 3 Distribution of Patients According to Follow-up

Duration of follow-up (months)	*No. of patients*
1–3	78
4–6	11
7–9	2
10–12	1

There was a low incidence of minor complications—mild haematuria, pain and infection; all of these complications resolved with conservative treatment. Ureteric perforation was rare and occurred in only 3 patients, all of whom responded to conservative management; 2 of these patients had endoscopic placement of ureteric double pigtail stents and the third patient was merely observed. No stricture complication was observed. There was no mortality in the series (Fig. 5).

Several factors were analysed and it was found that stone burden, as indicated by stone diameter, influenced the likelihood of success of stone fragmentation by laser. For stones that were successfully fragmented at the first procedure, the average diameter was 8.4 mm, in contrast to 13.4 mm for stones that required a second proce-

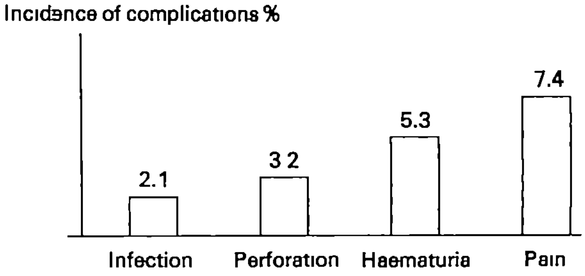

Fig. 5 Incidence and type of complications.

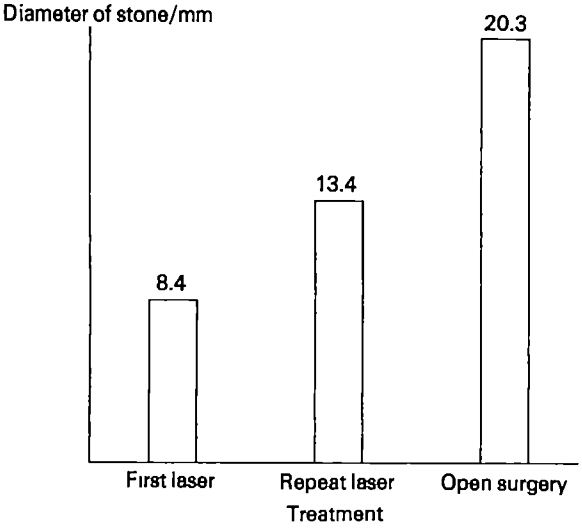

Fig. 6 Stone size versus mode of treatment.

dure. The average diameter of the stones which eventually required open surgery was 20.3 mm (Fig. 6).

The site of the stone in the ureter appeared to influence the likelihood of successful laser fragmentation (Table 4).

Discussion

The laser offers a few significant advantages over other modes of treatment for ureteric calculi—it is excellent for the treatment of impacted and intramural ureteric calculi and, with the use of a small calibre 7.2 F ureteroscope, it is highly effective for stones at all levels of the ureter. ESWL monotherapy *in situ* without stenting is less suitable for the impacted calculus because of the lack of the "expansion chamber" and the stone–water interface which is necessary for the shock wave to reach the stone. Ultrasonic and electrohydraulic lithotripsy may have a higher risk of causing ureteric mucosal injury and perforation when used for intramural or impacted ureteric calculi. This is because these modes require a higher level of energy to attain a similar fragmentation effect, and therefore the higher level of heat generated increases the risk of ureteric injury; laser fragmentation generates less heat because of the lower energy required, and at the operating wavelength of 504 nm the laser energy is maximally absorbed by most stones and minimally by ureteric tissue. Ultrasonic and electrohydraulic lithotripsy require the use of larger ureteroscopes, which may contribute to the risk of injury in the confined space of an impacted calculus or the intramural ureter. The laser fibre, however, delivered through the 7.2 F semirigid mini-ureteroscope, can be placed most advantageously in direct contact with the stone surface and fragmentation can be more precisely performed with a greater margin of safety.

Table 4 Stone Fragmentation Rates at Different Ureteric Sites

Site in ureter	*Total*	*Successful laser fragmentation*	*Open surgery*
Upper	22	20	2
Mid	23	22	1
Lower	55	55	0

In patients with obstructive Steinstrasse, the laser fibre can be used with great efficacy to initiate ureteric decompression by fragmenting and disimpacting the calculus fragments at the ureteric orifice, thus creating a foothold that allows further fragmentation and subsequent complete removal of the stones.

Zerbib *et al.* (1990) reported a fragmentation rate of 78.3% (36 of 46 ureteric stones) with the Pulsolith prototype laser lithotriptor, using a 250 μm flexible laser fibre with energy output of 80 mJ. Retrograde ureteroscopy was performed with rigid (11 and 9.5 F) and flexible ureteroscopes; the ureteric orifice was dilated to facilitate endoscopic access. There were 10 failures of laser lithotripsy in their study; 4 were due to laser dysfunction at the time of the procedure and 6 patients had laser-resistant pure calcium oxalate monohydrate stones. The 10 failures were treated by ultrasonic lithotripsy and stone basket extraction, and by push–bang (ESWL). There was no open surgery. No ureteric perforation was experienced in their series.

With the use of a first generation lithotriptor in the treatment of 227 ureteric calculi in 225 consecutive patients, Dretler (1990) experienced stone fragmentation rates of 64% by laser alone, 13% by laser with basket extraction and 15% by laser combined with ESWL. A lower energy of 60 mJ pulses was used, which may account for the lower stone fragmentation rate achieved by laser alone.

Bagley *et al.* (1989) had a stone fragmentation rate of 100% in the treatment of 70 ureteric calculi with the Technomed Pulsolith lithotriptor; 65% of these stones were composed of pure calcium oxalate monohydrate. In their series, the 400 μm laser fibre was also used—thereby delivering a higher level of laser energy, 200 mJ, with a theoretically greater chance of successful stone fragmentation.

In our experience, there was a lower incidence of minor complications—15% with no ureteric stricture. This was due to the smaller calibre of the semirigid 7.2 F mini-ureteroscope which permits relatively atraumatic and easy ureteric access with no need for ureteric dilatation. There were 3 cases (3%) of ureteric perforation which may be attributed to the element of the "learning curve" early in the series and possibly the higher level of laser energy used, *i.e.* 135 mJ. Three patients required open surgery because of failed fragmentation of their monohydrate stones. Theoretically, if the 400 μm laser fibre were used for these 3 particular patients, their stones could be fragmented. However, the working channel on our mini-ureteroscope was not able to accommodate the large diameter of the fibre.

Stone burden, in terms of stone diameter, affects the likelihood of a successful outcome with laser lithotripsy. The site of the stone in the ureter appears to affect the chance of success since there were different success rates in all thirds of the ureter; the success rates were 91% (20 of 22), 96% (22 of 23) and 100% (55 of 55) for stones in the upper, mid and lower ureters respectively. This resulted primarily from the easy ureteric access afforded by the mini-ureteroscope.

For upper ureteric stones our result compares favourably with the success rate of 88% reported by Morse and Resnick (1991) for *in situ* ESWL monotherapy with stenting using the Dornier HM3 lithotriptor; however, this method involves 2 separate procedures, *i.e.* stenting followed by shock wave therapy, whereas laser lithotripsy can be carried out in a single setting.

Laser lithotripsy for ureteric stones also gives superior results when compared with the other modes of endoscopic lithotripsy—a success rate of 91% for electrohydraulic lithotripsy was reported by Denstedt and Clayman (1990). Kostakopoulos *et al.* (1989) reported an overall success rate of 88.8% for ureterolithotripsy using ultrasound fragmentation, forceps extraction or a combination of the 2 methods. The success rates with regard to the level of the ureter were 38.5%, 51% and 95.5% for the upper, mid and lower ureters respectively.

Pulsed dye laser lithotripsy is a major technological advance in the treatment of ureteric stones. It is relatively atraumatic and safe and results in improved cost effectiveness in terms of low morbidity and a high success rate, thereby reducing the need for alternative or repeat procedures.

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Subtrigonal Phenol Injections in the Treatment of Idiopathic Detrusor Instability in the Female—a Long-term Urodynamic Follow-up

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Summary—A total of 36 subtrigonal phenol injections were performed on 29 patients with detrusor instability. Long-term follow-up (mean 13.7 months) showed a subjective response rate of only 14%, and objectively there was no significant change in any urodynamic parameter in the group as a whole. There was, however, a significant improvement in cystometric capacity and volume at first contraction, in those under 55 years of age. One patient developed a vesicovaginal fistula following repeat injections. This suggests that subtrigonal phenol injections have little place in the treatment of detrusor instability, especially in the over 55s, and repeat injections should be abandoned because of the risk of major complications.

Detrusor instability remains a common problem in the management of female urinary incontinence. In our own unit detrusor instability is present in 20% of patients in a pure or mixed form. The treatment of the condition remains less than satisfactory. Drug treatment is successful in a proportion of patients but even the best treatments have a poor response rate, often have significant side effects, and the relapse rate is high. Bladder re-training has been shown to help a considerable number of patients, but again relapse rates tend to be significant. Holmes *et al.* (1983) showed that 85% of patients were improved after bladder retraining, but that after 3 years this had fallen to 48%.

If non-invasive forms of treatment fail, one is left to consider surgical treatment for the patient with troublesome symptoms. Transvaginal sacral neurectomy (Warrell, 1977) and bladder distension (Pengelly *et al.*, 1978) have proved to be less than ideal and have been abandoned from most clinicians' practice.

Subtrigonal phenol injections for the treatment of detrusor instability were described by Ewing *et al.* in 1982. Their good results (overall 76% cure rate) were confirmed by others (Blackford *et al.*, 1984; Cameron-Strange and Millard, 1988), but recently other workers have suggested that the procedure is considerably less successful and not without considerable risks (Rosenbaum *et al.*, 1988; Wall and Stanton, 1989). All of these studies have relied upon symptomatic assessment of cure or failure and none has looked at the long-term cystometric change produced by the procedure. In this study we determine the urodynamic changes produced by phenolisation of the pelvic plexus and assess the benefits of the procedure in the long term.

Patients and Methods

A total of 36 subtrigonal phenol injections were performed on 29 patients with idiopathic detrusor instability between March 1986 and June 1990. All had previously undergone urodynamic investigation by either dual channel subtracted cystometry or videocystourethrography, and had failed to respond to drug therapy and/or bladder re-training. Urodynamic follow-up was obtained in 25 cases and subjective assessment was obtained in 34; 2 patients declined to attend for review.

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The technique of subtrigonal injection used is as described by Ewing *et al.* (1982). Our practice, however, is to inject 2 ml of normal saline initially on each side to ensure correct placement, and thereafter inject a further 6 ml of 6% aqueous phenol or as much as can be injected without producing excessive indentation of the bladder. A 14–16 F Foley urethral catheter is left *in situ* overnight and removed the following morning. When the patient is voiding satisfactorily she is allowed home.

Statistical analysis was performed using *t* tests except for the results of residual volumes, which were not normally distributed. These were analysed using the Wilcoxon matched pairs test.

Results

Duration of follow-up was between 1 and 40 months (median 11). The age range was 40 to 73 years (median 57). Subjective assessment showed an improvement rate of 14% after both a first or repeat injection. Table 1 shows the results for the filling phase of the cystometrogram, for all patients. There are no statistically significant differences between pre-treatment and post-treatment values. Tables 2 and 3 show the same parameters when subdivided by age; this demonstrates a better urodynamic outcome in the younger age group. Table 4 gives the results for voiding function. Numbers are smaller because many patients were unable to void either prior to or following, bladder filling. As results of residual volumes were normal, the small volumes voided prior to filling in the post-treatment group must indicate that their bladders were not full when they were asked to void. There were no statistically significant differences between pre-treatment and post-treatment values. Four patients developed a complication following phenolisation, 3 of them following a repeat injection. One patient had delayed voiding (4 days), 2 patients had persistently high residual volumes, and 1 patient developed a vesicovaginal fistula. The vesicovaginal fistula developed within a week of subtrigonal phenolisation in a patient undergoing repeat injections. In view of the fistula and her persistent severe detrusor instability she underwent urinary diversion; she is currently well.

Discussion

The finding that there is no overall, significant long-term subjective or urodynamic change following subtrigonal phenolisation suggests, as others have

Table 1 Results of Filling Cystometry Before and After Treatment

	First desire to void (ml)	*Volume 1st con. (ml)*	*Cystometric capacity (ml)*	*Maximum filling pressure (cmH_2O)*	*Maximum detrusor pressure (cmH_2O)*
Pre-treatment	171 (±129)	228 (±181)	315 (±169)	36.4 (±21.5)	44.3 (±18.1)
Post-treatment	201 (±135)	260 (±200)	357 (±195)	29.4 (±15.7)	38.0 (±14.1)
Significance	NS	NS	NS	NS	NS

Table 2 Results of Filling Cystometry Before and After Treatment for Patients Aged >55 years

	First desire to void (ml)	*Volume 1st con. (ml)*	*Cystometric capacity (ml)*	*Maximum filling pressure cmH_2O)*	*Maximum detrusor pressure (cmH_2O)*
Pre-treatment	150 (±121)	190 (±176)	284 (±159)	39.1 (±23.2)	42.2 (±22.0)
Post-treatment	142 (±101)	158 (±150)	273 (±200)	31.6 (±5.2)	38.7 (±11.3)
Significance	NS	NS	NS	NS	NS

Table 3 Results of Filling Cystometry Before and After Treatment for Patients Aged <55 Years

	First desire to void (ml)	*Volume 1st con. (ml)*	*Cystometric capacity (ml)*	*Maximum filling pressure (cmH_2O)*	*Maximum detrusor pressure (cmH_2O)*
Pre-treatment	194 (±139)	272 (±185)	347 (±179)	33.4(±20.2)	46.6 (±13.1)
Post-treatment	266 (±142)	381 (±189)	449 (±149)	26.9 (±16.6)	37.2 (±17.2)
Significance	NS	$P=0.01$	$P=0.01$	NS	NS

Table 4 Results of Voiding Function Before and After Treatment

	Free flow			*Voiding cystometry*			
	Peak flow rate (ml/s) (n=12)	*Voided volume (ml)* (n=12)	*Residual volume (ml)* (n=18)	*Peak flow rate (ml/s)* (n=18)	*Voided volume (ml)* (n=18)	*Maximum voiding pressure (cmH$_2$O)* (n=18)	*Residual volume (ml)* (n=18)
Pre-treatment	14.3 (±7.2)	258 (±211)	16.3 (±42)	12.0 (±4.2)	332 (±192)	35.2 (±21.1)	27.5 (±66)
Post-treatment	14.3 (±6.8)	161 (±112)	11.7 (±36)	14.0 (±63)	319 (±188)	30.0 (±16.6)	54.7 (±86)
Significance	NS	NS	NS	NS	NS	NS	NS

suggested recently (Rosenbaum *et al.*, 1988; Wall and Stanton, 1989), that the procedure has little to offer in the long term as a treatment of detrusor instability. Certainly we found that some patients noted a transient improvement in symptoms, but the vast majority reverted to their pre-treatment condition after a few days or weeks. There was often disparity between subjective and objective response where patients had an improvement in urodynamic parameters (1 patient actually reverted to a stable bladder), but were symptomatically unchanged.

Our finding of an improved response in the younger age group contrasts with the report by Blackford *et al.* (1984), who showed symptomatic success rates of 14 and 66% in the under 55 and over 55 age groups respectively. Cameron-Strange and Millard (1988), however, reported a slightly better subjective response rate in younger women. It is difficult to explain this disparity, and indeed why the younger age group should have a better response to the procedure.

Vesicovaginal fistula formation following the treament has been reported previously (Nordling *et al.*, 1986; Wall and Stanton, 1989), as has rectovaginal fistula formation (Cameron-Strange and Millard, 1988). We can say therefore that fistula formation is a recognised complication of the procedure, and given that all 3 vesicovaginal fistulae reported developed following repeat injections, we would suggest that the practice of repeating subtrigonal phenol injections be abandoned.

It appears therefore that phenolisation of the pelvic plexus, like many of the more minor surgical procedures employed, cannot be looked upon as the answer in the treatment of refractory detrusor instability. Transvaginal sacral neurectomy, bladder overdistension and bladder transection have all been introduced with enthusiasm only to be abandoned by many because of poor response or high relapse rates (Warrell, 1977; Pengelly *et al.*, 1978; Mundy, 1983). It may be that the time has come for us to consider earlier use of augmentation cystoplasty. The success rate is high (Mundy and Stephenson, 1985) and most patients sorely troubled by urge incontinence will accept the risks of major surgery, and the likelihood of requiring to self-catheterise, if there is a real chance of their being rendered continent.

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Complications of Clam Enterocystoplasty with Particular Reference to Urinary Tract Infection

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Summary—A study was carried out on 112 patients who had undergone a clam procedure. Follow-up extended from 15 months to 8 years. The efficacy of the operation in achieving and maintaining continence in patients with instability and hyper-reflexia was confirmed (93% in the neuropathic group, 91% in the congenital instability group and 78% in the idiopathic group).

Complications were common and included inability to void (requiring self-catheterisation), haematuria, mucus production and recurrent urinary tract infection. Complete bacteriological data were obtained on 80 patients; 30% were infected pre-operatively (all but 4 in the neuropathic group) but 66% had bacteriuria at the time of assessment after surgery. Subjectively, 17 patients (24%) who "never" got infected had bacteriuria, as did 29 (63%) of those who were "occasionally" infected. Objectively, 84% of patients on intermittent self-catheterisation (ISC) had positive cultures, but even in those voiding spontaneously bacteriuria was present in 60%.

Careful follow-up of these patients is mandatory and a more rigorous approach to eradication of infection and subsequent prophylaxis has been instituted.

Much has been written about the merits of the clam procedure since it was first described by Bramble (1982). It has stood the test of time for the treatment of recalcitrant detrusor instability and for both poor compliance and hyper-reflexia in the neuropathic bladder. Most authors have focused mainly on the success of the procedure in achieving continence, which should approach 90% (Mundy and Stephenson, 1985; McCrae *et al.*, 1987) and most urological centres, especially in the United Kingdom, have adopted the technique, mainly for idiopathic instability with urge incontinence, though not always with such good results (George *et al.*, 1991). However, with the notable exception of the possible malignant potential of both the clam procedure and substitution cystoplasty and their association with infection and N-nitrosamines described by Nurse and Mundy (1989), nothing has been written about the incidence and morbidity of urinary tract infection in ileal augmentation cystoplasty.

Patients and Methods

A total of 112 patients underwent the clam procedure between 1983 and March 1990. An assessment of continence and voiding technique was obtained on all patients (Table 1). They ranged in age from 8 to 67 years, with the majority aged between 10 and 45 years (Fig. 1); 42 were overtly neuropathic, mostly with myelodysplasia, 36 had idiopathic instability and 34 had congenital nocturnal/diurnal enuresis. Complete subjective and objective data on complications were obtained in 80 patients, with particular emphasis on bacteriuria and urinary tract infection.

Table 1 Details of Patients

Aetiology	*Continence achieved (%)*	*Voiding by ISC (%)*
Neuropathic group (42)	39 (93)	18 (43)
Idiopathic group (36)	28 (78)	8 (22)
"Congenital" group (34)	31 (91)	10 (30)

Read at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

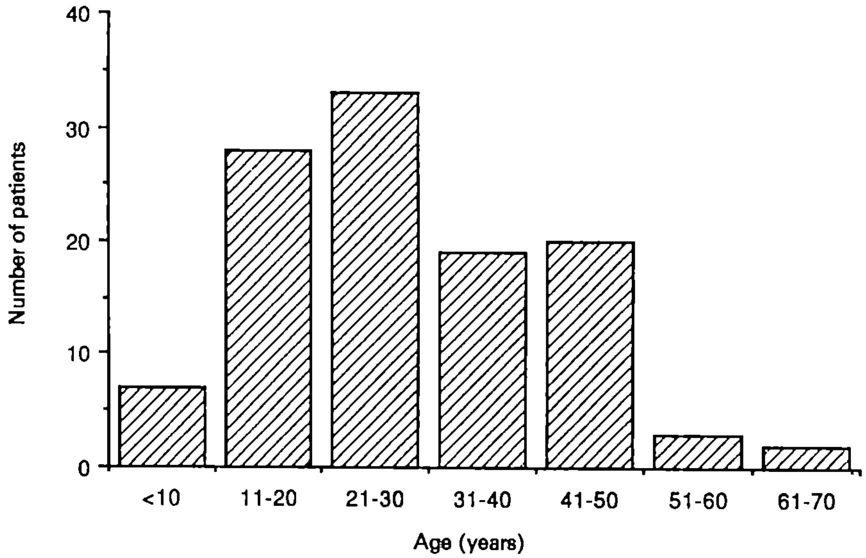

Fig. 1 Age distribution of patients.

Results

The results in a smaller group of patients have been described in detail by Lewis *et al.* (1990). Apart from 3 patients in the idiopathic group who had undergone previous colposuspension, there were no urodynamic factors which predicted the likelihood of ISC being necessary in either of the non-neuropathic groups. Equally, there were no factors, urodynamic or otherwise, to explain the failures.

The commonest complications were urinary tract infection and bacteriuria; 24 patients (30%) had positive cultures pre-operatively, though all but 4 of these were in the neuropathic group. Overall this figure rose to 63%. The likelihood of infection was partially dependent on the method of voiding, being highest in patients on ISC (84%), lowest in patients voiding spontaneously and 65% in patients voiding by activation of the artificial sphincter (all in the neuropathic group).

In order to assess the occurrence of asymptomatic bacteriuria, patients were questioned about the frequency or otherwise of urinary infection (Table 2) and it was notable that two-thirds of those with only occasional clinical infection had bacteriuria at the time of assessment.

Escherichia coli was the commonest organism (78%) and, surprisingly, in view of the preponderance of neuropathic patients, only 2 patients had *Pseudomonas* infections and only 4 patients infected before surgery had a different organism post-operatively; 28 patients (34%) complained of intermittent macroscopic haematuria and two-thirds of these had bacteriuria.

Table 2 Urinary Tract Infection in 80 Patients

Subjective infection rate (post-operative)		%
Never (21%)	positive culture	24
	sterile	76
Occasional (36%)	positive culture	66
	sterile	34
Frequently (43%)	positive culture	80
	sterile	20

Over half of the patients (57%) complained about mucus production and many felt this was aggravated by infection. Less than half of them wanted treatment other than antibiotics and in only 3 cases were bladder washouts required.

In 3 patients the artificial urinary sphincter was removed because of erosion, and 3 patients developed spontaneous rupture at their stitch line. Although hardly a complication, there were 12 successful pregnancies in the group, including one Caesarean section and one set of twins.

Discussion

It is recognised that bacteriuria is common in patients with ileum incorporated into the bladder and even commoner when large bowel substitution of the bladder has been performed (Nurse and Mundy, 1989). In the short term, in patients with clam ileocystoplasties there is a significant morbidity associated with clinical infection, especially in the group practising self-catheterisation, where mucus production is an additional problem. For this reason alone, rigorous attempts to eradicate infection and institute prophylaxis seem appropriate but likely to be unsuccessful in many patients. In the longer term, the potential risk of tumour development haunts us (Stone *et al.*, 1987).

Theoretically, the risk of tumour formation ought to be higher in patients with caecocystoplasties, where bacteriuria is commoner and N-nitrosamine levels higher (Nurse and Mundy, 1989), but this has not proved to be the case.

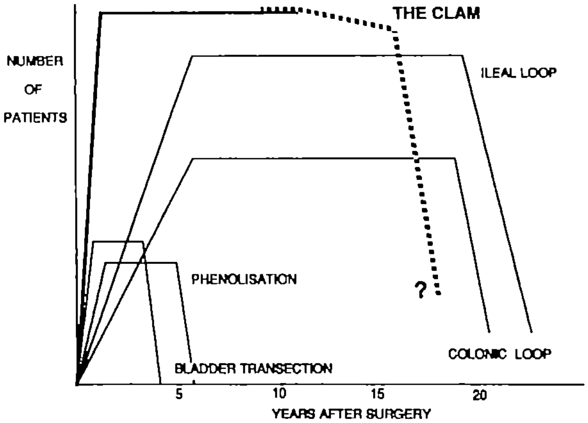

Fig. 2 Urological procedures.

At the moment it is impossible to assess the likelihood of tumour formation in clam patients, but the technique is being used so widely and on young patients that alternative techniques must continue to be sought.

Surgery abounds with techniques that have stood the test of time for varying periods (Fig. 2). We must hope that if and when the clam procedure is abandoned, it will be because alternatives have been developed and not because of a spate of tumours.

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Squamous Cell Carcinoma of the Urinary Bladder

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Summary—A series of 52 patients with squamous cell carcinoma of the urinary bladder were studied over a 6-year period. They constituted 27% of all bladder tumours. The male: female ratio was 12:1; 62% of the patients were below the age of 50 years (mean 47) and 31% had a previous history of urinary bilharziasis. Associated stigmata of *Schistosoma haematobium,* as sandy patches, were detected in 69% of patients. Fourteen had bilharzial ureteric strictures as seen on intravenous urography and most of the tumours occurred in the region of the trigone; 60% had T3 N0 M0 tumours at presentation. Eighteen patients received radical radiotherapy and 16 patients under the age of 55 years underwent radical cystectomy with diversion of urine to an isolated rectum. The 5-year survival rate in the radical cystectomy group was 75%. Other modalities of treatment and their results are discussed.

Squamous cell carcinoma of the urinary bladder constitutes approximately 3% of all bladder tumours in Western countries (Sarma, 1970) but is reported to constitute 65 to 67% in Egypt (El Boulkany *et al.*, 1972) and Iraq (Talib, 1970), where urinary bilharziasis is endemic. A close relationship between urinary bilharziasis and squamous cell carcinoma of the urinary bladder was suggested by Hashem (1961) and Shamma (1955). However, Payet (1962) found no convincing evidence to support this claim.

We report the pattern of squamous cell carcinoma of the urinary bladder in Sudanese patients seen in 4 urological centres in Khartoum over a 6-year period.

Patients and Methods

A study was made of all patients with squamous cell carcinoma of the urinary bladder presenting to the urological centres in 4 teaching hospitals in Khartoum between January 1984 and January 1990. All were screened for urinary bilharziasis by obtaining a previous history of urinary bilharziasis and testing 5 consecutive morning urine samples for bilharzial ova. Investigations included urine analysis for evidence of infection, serum creatinine, blood urea and intravenous urography (IVU) with post-micturition views. Cystoscopy was performed under general anaesthesia to detect stigmata of urinary bilharziasis, as well as for clinical staging, macroscopic appearance and biopsy of lesions for histological confirmation. Follow-up ranged from 1 to 6 years (mean 3.5).

Results

Of 196 patients with bladder cancer, 52 had squamous cell carcinoma (26.5%). There were 48 males and 4 females with a male:female ratio of 12:1 and a male predominance in all age groups. Their ages ranged between 20 and 84 years (mean 47); 32 patients (62%) were below the age of 50 years and 31% had a past history of urinary bilharziasis. The time lapse between first infestation with urinary bilharziasis and presentation with bladder cancer was 10 to 15 years. The commonest presenting symptom was haematuria; this occurred in 96% of patients and was described as painless in 82%. Eighteen patients presented with a suprapubic mass and 14 had obstructed kidneys. The cystographic phase of the IVU detected an irregular filling defect consistent with bladder cancer in 89% of cases. This was associated with bilharzial ureteric

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stricture in 14%, vesical calculi in 12% and the bladder was small and contracted in 2%. Cystoscopy revealed the tumour in all cases. The tumour occurred in the region of the trigone and the posterior bladder wall in 26 patients, in either lateral wall in 14, in the region of the bladder neck in 3 and was multiple in 9. Evidence of urinary bilharziasis was found in 36 patients (69%); this appeared as sandy patches in 29, bilharzial tubercles in 4 and cystitis cystica in 3; 60% of patients had T3 NO MO tumours at presentation, 30% had either T1 NO MO or T2 NO MO tumours and 10% had TX N1–3 MO or TX N4 M1 tumours. Exact clinical staging was often difficult because of the dense involvement of the perivesical tissues in the process of bilharzial uropathy. The different modes of treatment are shown in Table 1. Eighteen patients (36%) with T3 NO MO tumours at presentation underwent radical radiotherapy as the sole method of treatment. Eight patients in this group were young, suitable for surgery and were offered radical cystectomy, but refused. Radical cystectomy was performed in 16 patients with T2 NO MO or T3a NO MO tumours at presentation. All were aged less than 55 years. The ureters were diverted to an isolated rectum with terminal colostomy in 15 patients and to an ileal conduit in 1. Six patients with T1 NO MO or T2 NO MO tumours underwent transurethral resection; this was followed by radiotherapy in 4 on reviewing the histology of the resected specimen. Salvage cystectomy was performed in 3 patients with bleeding or toxic manifestations. Another 5 patients with advanced disease underwent aggressive transurethral resection (mean resected tissue 60 g) to minimise toxic symptoms, bleeding or the passage of necrotic tissue. Forty patients were followed up for up to 5 years. The overall mortality at the end of the fifth year was 34.5%. The results of the different methods of treatment are shown in Table 2. The 5-year survival rate in the group who had radical cystectomy was 75%. All patients who had salvage cystectomy or palliative transurethral resection died within 5 years.

Table 1 Methods of Treatment in 52 Patients with Squamous Cell Carcinoma of the Bladder

Treatment	*No. of patients*	*(%)*
Radical radiotherapy	18	(35)
Radical cystectomy	16	(31)
Transuretheral resection + radiotherapy	6	(12)
Salvage cystectomy	3	(6)
Palliative transurethral resection	5	(10)
No treatment	4	(8)
Total	52	(100)

Table 2 Results of Treatment 5 Years Later in 40 Patients* with Squamous Cell Carcinoma of the Bladder

Treatment	*No of patients*	*Recurrence*	*Death*
Radical radiotherapy	16	4	5
Radical cystectomy	16	1	4
Transurethral resection + radiotherapy	4	3	0
Salvage cystectomy	2	2	2
Palliative transurethral resection	2	2	2
Total	40	12	13

* 12 patients were lost to follow-up

Discussion

Squamous cell carcinoma constituted 26.5% of all bladder tumours seen over a 6-year period. This is higher than the 6.2% reported from England (Pugh, 1973) but is low when compared with the 66% reported from Egypt (El Boulkany *et al.*, 1972) or the 65% from Iraq (Talib, 1970). The reason for the relatively low incidence of squamous cell carcinoma in this study, despite the high infestation rate with urinary bilharziasis, may be related to the fact that most of the patients living in endemic areas receive antibilharzial treatment frequently and from an early age. Alternatively, urinary bilharziasis is known to run a more benign course. There was a male predominance in all age groups and this is in agreement with a report from Egypt (Hashem, 1961). This is mainly due to the fact that males are more prone to infestation by urinary bilharziasis by virtue of their work on farms. In the present series, 31% of patients had a past history of urinary bilharziasis. Talib (1970) reported a past history of bilharziasis in 56% of his patients. The exact time lapse between the first infestation with urinary bilharziasis and the development of cancer is not known but is usually long because most patients contract the disease at an earlier age. The average age at presentation in this series was 47 years. Hashem (1961) from Egypt reported an average age of 44 years. The high frequency of bladder cancer in the younger age group is mostly attributed to the high incidence of urinary bilharziasis in younger patients. In all, 96% of patients presented with haematuria, which was painless in 82%. Although haematuria is the commonest symptom, and can be the only presentation of urinary bilharziasis, patients who develop bladder cancer in addition to bilharziasis do not always appreciate the development of newer symptoms and they attribute the haematuria to bilharziasis. Accordingly, most of them present with advanced disease. This partly explains the large number of patients presenting with a suprapubic mass (18%). The cystographic phase of the IVU detected bladder cancer in 89% of patients, compared with 38% from the Bristol Bladder Registry (Miller *et al.*, 1969). This could also be explained by the late presentation in this series. Associated bilharzial ureteric strictures occurred in 14% of patients and Hanash *et al.* (1984) reported an association in 93% in Saudi Arabia; 28% of the tumours occurred in the region of the trigone and posterior wall of the bladder, which are mostly affected in the process of urinary bilharziasis. The occurrence of squamous cell carcinoma in the younger age group, its predominance in male farmers, a past history of urinary bilharziasis, associated ureteric strictures and evidence of bilharziasis at cystocopy, all suggest a correlation between bilharziasis and squamous cell carcinoma. A similar correlation was reported from Egypt and Iraq (Talib, 1970; El Boulkany *et al.*, 1972). Although the exact role played by bilharziasis in cancer is still controversial, 2 sources of urinary bladder carcinogens have been proposed in *Schistosoma haematobium* (Abul Nasr *et al.*, 1962). Hashem (1961) produced evidence supporting an association between urinary bilharziasis and squamous cell carcinoma based on epidemiological, clinical and morphological grounds. Other workers have challenged this theory. For example, bladder cancer is less common in some African countries despite the fact that schistosomiasis is endemic. Dodge (1962) found only one case of vesical schistosomiasis in 81 bladder cancers. Furthermore, in Uganda, squamous cell carcinoma is the commonest histological type of bladder cancer even when there is little or no schistosomal infection. This is thought to be related to urinary obstruction caused by urethral strictures (Dodge, 1962). With regard to the statistical relationship between bladder cancer and schistosomal endemicity, it has been argued that the host-parasite relationship might differ in terms of genetic experience and susceptibility and that not only the presence but also the severity of infection should be considered (Higginson and Dettle, 1962).

Many patients suitable for radical cystectomy have refused this treatment on learning that it will be coupled with diversion of urine. The choice of a rectal bladder seems suitable for our patients, since an ileal conduit is socially unacceptable and the care of a colostomy is easier. The 5-year survival rate for patients with radical cystectomy was 75%. This is comparable to the rate reported by Ghoneim *et al.* (1972), who recommended radical cystectomy for clinically operable cases of bilharzial bladder cancer in Egypt. Other arguments in support of radical cystectomy are that squamous cell cancers are radio-resistant, that many patients are young, that cystoscopic follow-up following other modalities of treatment is often difficult and that radiotherapy can aggravate ureteric obstruction in most patients, who already have some degree of ureteric obstruction due to bilharzial ureteritis.

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Ethics, Logistics and a Trial of Transurethral versus Open Prostatectomy

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Summary—An increased long-term morbidity rate after transurethral compared with open prostatectomy has recently been claimed on the basis of retrospective studies of operations done up to 20 years ago. These studies have led to a demand for a prospective trial. Most reports show that peri-operative mortality following prostatectomy is virtually confined to unfit men over 80 years old. Before agreeing to participate in a trial we examined our operative mortality in this group of patients. Between 1981 and 1987, 123 octogenarians underwent transurethral prostatectomy: 64 operations were elective and 59 were performed for retention. There were 2 operative deaths (1.6%), both from gram-negative septicaemia despite prophylactic antibiotics. There were no additional deaths in the first 12 months following surgery. Few of these patients would have been considered fit to undergo an open prostatectomy. Any proposed randomised trial would have to exclude such high risk patients until it can be shown that open prostatectomy is equally safe.

Until 30 years ago an open operation was the standard method of prostatectomy in the United Kingdom and it took a decade or more before transurethral resection of the prostate (TURP) was accepted as a reasonable alternative. Initially, TURP was restricted to small glands and to patients who were old and unwell. Endoscopic surgery had the advantages of a lower operative mortality rate and a shorter hospital stay. Its disadvantages were that it was difficult to learn, required special training and, if done incompletely, often needed revision.

The advent of TURP made it possible to offer prostatectomy to many more patients, but even so it was not difficult to demonstrate its lower mortality. In 1967 O'Flynn, from the Meath Hospital in Dublin, published a meticulously documented study of 3083 patients operated on between 1954 and 1966 with an overall mortality rate of 2.8%. Almost all of the deaths were in patients aged over 70. The mortality rate for TURP was 1.2% in the 1597 men compared with 5.1% in 941 patients undergoing open surgery. In a review of the literature, Blandy (1971) reported a mortality rate of 1.2% in 26,048 TURPs in contrast to 3.3% in 10,455 open prostatectomies.

With continuing advances in anaesthesia and post-operative care, the hazards of all operations progressively fell until it became difficult to see any difference between the risks for TURP and open operation except in the very old and unfit. In 1973 Singh *et al.* confirmed that the mortality for TURP (7.6%) in the elderly was still less than that for open prostatectomy (9.2%). Sach and Marshall (1977) reported a 9% mortality rate by 3 months in octogenarians undergoing prostatectomy (mostly by an open technique) in contrast to 2.9% in patients aged less than 80.

The widespread recognition of the extra safety of endoscopic surgery coincided with a greater number of specialist urologists and an increase in the proportion of prostatectomies performed transurethrally, which had risen to 95% in this department by 1978 (Chilton *et al.*, 1978). This proportion was still less than in some North American centres, where the mortality was also appreciably lower. Mackenzie (1973) offered TURP to 99% of his patients with a mortality rate of 0.4%. More recent

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studies report mortality rates for TURP ranging between 0.2% (Mebust *et al.*, 1989) and 0.5% (Kolmert and Norlen, 1989). In the United Kingdom there continues to be an increased mortality in the very old: Wyatt *et al.* (1989) reported 7 deaths within 3 months in 94 patients aged more than 80.

In view of the pressure to participate in a prospective study, we thought it appropriate to review the place of TURP in the elderly in our own practice, and in particular to determine if any of them could have been entered into a trial of TURP versus open prostatectomy.

Patients and Methods

All patients undergoing prostatectomy at the Royal London Hospital between 1981 and 1987 were identified through the records of the Department of Pathology. The case records of 123 patients over the age of 80 years (mean age 83; range 80-89) were reviewed. All had been followed up for a minimum of 12 months or until death; 64 patients (52%) had elective surgery and 59 (48%) were admitted in urinary retention.

Twenty patients in the series (mean age 86 years) were admitted from a neighbouring psychogeriatric unit with various degrees of dementia, wearing an indwelling catheter for chronic retention with overflow. After careful consideration and discussion with their relatives, TURP was offered to these men with some reluctance in view of the risk of causing incontinence. However, a significant factor in making the decision was often that they could be lodged in sheltered accommodation if they were incontinent, but not with an indwelling catheter; 6 of these men had undergone an unsuccessful trial of a prostatic stent in the hope of avoiding an operation.

Results

All of the patients were treated by TURP. The mean weight of prostate resected was 20 g (range 5–80). Almost half of the series (60 patients) had a spinal anaesthetic. There were 2 peri-operative deaths (1.6%). Both of these patients (aged 82 and 84) had been admitted in acute urinary retention and were operated on within 48 h; the serum creatinine in both cases was normal and the urine sterile. Because they had been catheterised both were given prophylactic gentamicin, despite which they developed gram-negative septicaemia, became shocked and died within 36 h. There were no additional deaths within 12 months of the operation.

A total of 37 patients (31%) stayed on the surgical ward for less than 7 days; 76 (62%) were hospitalised for less than 14 days but 15 (12%) for more than 1 month; 99 men were discharged to their original domicile, 12 went to sheltered accommodation and 10 to a long-stay geriatric unit. Two months after surgery, 106 patients (88%) were voiding normally, 9 (7%) required a sheath and 6 (5%) a long-term catheter.

Discussion

In a recent comprehensive review, Neal (1990) concluded that both TURP and open prostatectomy have their respective roles to play in the treatment of men with outflow obstruction. However, we have been unable to find any contemporary series that includes a substantial number of octogenarians subjected to open surgery with a mortality rate that compares to that of TURP.

The data upon which Roos *et al.* (1989) have called into question the safety of TURP reveal that many of their patients were operated upon during years when TURP was still being introduced and the proportion of patients who were offered endoscopic surgery was substantially less than in many specialised urological units. Of crucial significance is the reason why a surgeon would advise an open operation rather than a TURP. In their retrospective study of the case records of 485 of the Manitoba patients, Malenka *et al.* (1990) could find no consistent difference in the risk factors, *e.g.* cardiovascular disease, in the 2 groups of patients. Why then was one offered a TURP and another an open operation? In that era surgeons would select the operation with which they were most familiar, and many preferred an open operation because they were not comfortable with TURP in large glands.

The reason for the increased morbidity (from cardiovascular disease) which Roos *et al.* (1989) found in the follow-up of men who had undergone TURP is uncertain. One possible variable (for which there are no data) is the type of irrigant fluid used during the resection. Although an isotonic solution, such as glycine, with its low risk of absorption and haemolysis is mandatory today, 20 years ago many urologists used water (Emmett *et al.*, 1969).

Roos *et al.* (1989) have demanded that the question of transurethral versus open prostatectomy be put to a randomised prospective trial, and such a study will shortly be undertaken under the aegis of the American Urological Association (AUA) (Holtgrewe, 1990). It is therefore necessary to consider how to obtain fully informed consent from a patient (or his relatives) about to undergo such an operation. When the risk of any prostatectomy is so small, particular care needs to be taken to explain the need for this trial to the 80-year-old man in whom, as present evidence suggests, there is a considerably increased chance of dying if he has an open operation.

The protocol of the proposed AUA trial of open prostatectomy versus transurethral resection has been very carefully designed to exclude patients with identifiable risk factors. Most prostatectomies in the United States are undertaken for relief of symptoms, not for acute or chronic urinary retention. Patients with an indwelling catheter will be excluded from the trial, as will those with urinary tract damage, severe infection and recurrent bleeding (Holtgrewe, 1990). Patients in greatest jeopardy will not be randomised and will still, presumably, undergo a TURP. The design of this trial seems implicitly to accept the extra safety of TURP.

Our current policy is to offer TURP to geriatric patients, even those with dementia, unless it seems certain that they will not survive the operation. Even 20 years ago, Mackenzie (1973) considered that almost every man who could tolerate a spinal anaesthetic could withstand a TURP. It is likely that many elderly patients who undergo a successful TURP would not have been fit enough to be offered an open operation with its greater operative morbidity (Chisholm, 1989). Moreover, few octogenarians have such a long prognosis that the risk of a second operation would be very relevant.

It is difficult to see how a randomised trial of TURP versus open prostatectomy could be devised without deliberately excluding high risk elderly patients. To the relatively young and healthy patient, a more attractive idea would probably be to participate in a trial of some entirely non-operative technique (McLoughlin and Williams, 1990)—an option that has been written into the proposed AUA study. It will be interesting to learn how many fit men will choose to enter a trial, one arm of which includes an open procedure which is withheld from patients at extra risk because it is generally regarded as being simply less safe.

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A Self-administered Patient Questionnaire in the Assessment of Symptoms before and after Prostatectomy

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Summary—A self-administered patient questionnaire was developed to assess the severity of key symptoms before and after transurethral prostatectomy (TURP). This questionnaire was validated by comparison with a standard assessment performed by the doctor. Complete data were obtained on 39 men studied before and 3 months after prostatectomy.

Close associations were found between the scores resulting from the assessments performed by the patient and those carried out by the doctor. These associations were found for individual scores and for aggregate scores for obstructive and irritative symptoms before and after operation.

Symptom scores after operation were significantly related to the patients' overall assessment of whether the operation had been a success—a low score being associated with a satisfactory outcome. It is suggested that self-administered symptom questionnaires can give a reliable picture of the outcome of prostatectomy and might be useful in developing audit systems.

Although prostatectomy is one of the most common elective surgical procedures, with between 10 and 20% of men in their forties subsequently undergoing this operation (Lytton *et al.*, 1968; Glynn *et al.*, 1985), there still exists uncertainty over the outcome (Fowler *et al.*, 1988; Roos *et al.*, 1989). The outcome of an operation can be expressed in a number of ways, including the incidence of serious complications, the necessity to repeat the procedure, general improvements in health status or, most commonly, in the relief of symptoms. Several attempts have been made to assess the outcome of prostatectomy using these methods. Most studies have found that 70% to 80% of men have a satisfactory symptomatic outcome (Neal *et al.*, 1989) and that the mortality and morbidity rate in specialised units is very low (Mebust *et al.*, 1989). On the other hand, some studies have found little improvement in the quality of life after the operation (Fowler *et al.*, 1988) and 1 study even found that transurethral prostatectomy was associated with increased long-term mortality compared with open prostatectomy (Roos *et al.*, 1989).

Measures of symptom relief typically include a professional assessment of the patient's condition. It is generally accepted that certain urological symptoms are associated with outflow obstruction and may respond well to prostatectomy; the problem for the urologist is that many of these symptoms may also be caused by other urological conditions such as detrusor instability. Standard questionnaires and scoring systems have been developed to assess symptoms before and after prostectomy (Frimodt-Moller *et al.*, 1984). These can be used to show significant improvement after operation and compare well with other subjective and objective measures of outcome (Neal *et al.*, 1989).

The potential disadvantages of such scaling questionnaires include the following:

(1) It takes time to administer to patients.
(2) There may be problems of reliability between different assessors.

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(3) The scale is assessed by the doctor and it may well be that the patients' perceptions of their condition differ from those of the doctor.

In an attempt to overcome these problems, we designed a questionnaire based on the Frimodt-Moller scaling questionnaire, but one which could be completed by the patient. We have carried out a prospective study of men undergoing prostatectomy who were studied before and after operation. The new questionnaire was compared with a standard questionnaire and with the subjective outcome of the operation as viewed by the patient.

Method

The self-administered patient questionnaire (Appendix) was developed and tested on patients undergoing elective prostatectomy. The questions were related to the symptoms documented in a standard questionnaire (Frimodt-Moller *et al.*, 1984). The wording of the questionnaire was tested on patients and found to be understood across social groups. The results of the self-administered questionnaire were compared with assessments of the same patients by 1 of 2 doctors using the traditional scale (Frimodt-Moller *et al.*, 1984).

The patient-completed questionnaire was given to 50 successive in-patients and the doctor completed the standard questionnaire form. Three months after operation, patients were sent a copy of the questionnaire and were asked additional questions relating to their perception of the outcome of the operation. The doctor's assessment was repeated in the Out-patient Department but in a few cases this was completed over the telephone.

There were 39 patients on whom complete data were collected; these included paired questionnaires from both patient and doctor before and after operation and the patient's view of the outcome of the operation. The scores on all questions were converted to a similar scale by expressing them as a proportion of the total and quoting them as a range from 0 to 1. Higher scores indicate more severe symptoms.

Statistical assessment was performed by non-parametric statistical methods including Kendall's tau as a measure of correlation, the Kruskall-Wallis analysis of variance by ranks to assess differences between several groups, and differences between paired data were assessed by means of Wilcoxon's paired test (Blalock, 1979). The association between the 2 questionnaires—that of the doctor and the patient—was measured by plotting the data according to the method of Bland and Altman (1986).

Results

Comparison of individual items

Table 1 compares the responses of patient and doctor for individual items in obstructive and irritative categories for both pre- and post-operative scores. The 2 responses were compared using Kendall's tau as a measure of association. In all except 1 item (the strength of the urinary stream), the 2 responses were significantly associated. The proportion of cases where doctor and patient gave exactly the same score varied for the different questions from 22/39 (56%) to 38/39 (97%).

There was a tendency, particularly after operation, for the patient to score his symptoms higher than did the doctor. However, this was only

Table 1 Comparison of Responses by Patient and Doctor for Individual Items before and after Operation

			Pre-operative scores				*Post-operative scores*			
Item		*No of categories*	*Ties*	*Doctor > Patient*	*Patient > Doctor*	*Tau*	*Ties*	*Doctor > Patient*	*Patient > Doctor*	*Tau*
Irritative symptoms	Frequency	4	22	13	4	0.65**	28	6	5	0.59**
	Nocturia	4	33	4	2	0.87**	30	3	6	0.73**
	Enuresis	2	36	1	2	0.49**	38	0	1	0.70**
	Urgency	4	26	4	9	0.60**	20	2	17	0.52**
Obstructive symptoms	Stream	4	22	11	6	0.32 (ns)	30	4	5	0.49**
	Hesitancy	2	25	1	13	0.66**	25	4	10	0.42**
	Bladder emptying	2	33	2	1	0.67**	33	4	2	0.49**

Measure of association = Kendall's tau.
** significant ($P < 0.01$).
(ns) = Not significant

statistically significant for the symptoms of urinary urgency.

Comparison of aggregate scores

Table 2 presents the mean aggregate obstructive and irritative scores before and after the operation for both the patient and doctor assessment. Once again, there was only 1 category (the post-operative assessment of irritative symptoms) where the scores of the patient and doctor differed significantly, the patient scores being higher. There were significant associations between all of the scores as shown by the values for Kendall's tau and the rank ordering of scores was essentially the same.

Using the methods described by Bland and Altman (1986), we determined how close the association was between the 2 questionnaires. This method compares the mean difference of the 2 scores with the 95% confidence interval of the difference (× 2 the SD of the difference). One would therefore expect 95% of observations to fall within these limits and this was the case for the pre-operative assessments. However, more than 5% of the observations fell outside these limits for the post-operative scores for obstructive symptoms and combined categories (obstructive + irritative). This was probably due to "end" effects using this scale because a high proportion of patients recorded minimum scores (0): for example, after operation 40% of the obstructive symptoms scores were zero. It was for this reason that non-parametric tests of significance were used.

Comparison of pre- and post-operative scores

Table 3 shows the mean change in score after operation compared with the score before operation. Scores after operation were significantly lower than the pre-operative assessment for all categories of symptoms, indicating that both scales were sufficiently sensitive to identify the general improvement in symptoms following surgery. When the mean differences between the scores measured by doctors or patients were compared, the change in irritative symptoms scored by the doctors was significantly greater than that scored by the patients. This suggests that the patients were less

Table 2 Comparison of Scores from Self-administered Questionnaire (patient) and Doctor's Assessment (shown as means (standard deviation) standardised to range from 0 to 1)

Mean (standard deviation)	*Patient*	*Doctor*	*Difference (Doctor-Patient)*	*Kendall's tau-b*	*No. outside repeatability*
Before surgery (n = 39)					
Irritative	0.480 (0.192)	0.495 (0.237)	+0.005 (ns)	0.81**	2
Obstructive	0.608 (0.272)	0.523 (0.190)	−0.085 (ns)	0.46**	2
Combined	0.543 (0.193)	0.509 (0.175)	−0.034 (ns)	0.59**	2
After surgery (n = 39)					
Irritative	0.280 (0.241)	0.208 (0.188)	−0.072*	0.68**	2
Obstructive	0.154 (0.224)	0.146 (0.183)	−0.008 (ns)	0.35**	4
Combined	0.217 (0.196)	0.177 (0.164)	−0.030 (ns)	0.67**	5

* $P < 0.01$ Wilcoxon rank sum
** $P < 0.05$.
(ns) = Not significant.

Table 3 Change in Scores after Operation and Significance of Differences between Changes in Doctors' and Patients' Scores

Mean (standard deviation)	*Change in patient score*	*Change in doctor score*	*P*
Irritative	0.200** (0.235)	0.287** (0.246)	0.001
Obstructive	0.453** (0.276)	0.377** (0.239)	0.232
Combined	0.327** (0.207)	0.332** (0.200)	0.655

** $P < 0.001$ difference between pre- and post-operative scores sanguine than the doctor about their residual irritative symptoms. No such differences were observed for the combined scores (obstructive+irritative) or the obstructive symptoms alone.

Comparison with patients' overall assessment of success

Ideally, the relative merits of the 2 scores should be compared with an external measure of success. There is, unfortunately, no such ideal method. We asked the patients for their view about the outcome of the operation on a five-point scale ranging from successful (asymptomatic) to worse than before operation (Neal *et al.*, 1989). The relative success of the symptom scores derived from either the patient's or doctor's questionnaire in differentiating patients with a successful outcome from those with a less successful outcome was tested using the Kruskall-Wallis analysis variance of ranks. Table 4 shows the mean ranks of various scoring combinations for the separate categories of the patients' overall assessment. In general, significantly lower post-operative symptom scores obtained both by the patient-based or doctor-based scoring systems were found in patients who had a satisfactory outcome. Patients who felt that the results of the operation were not satisfactory overall had greater post-operative symptoms scores than those who felt much better. The combined score (obstructive+irritative) performed better than the individual component scores.

When the changes in symptom score after operation (pre-operation scores minus post-operative scores) were examined they were found to be independent of the patient's perceptions of success. It appears, therefore, that the general rating applied by patients after the operation equates more with the state of their symptoms at that time than with any improvement that may have been observed due to the operation. Although it was observed that patients with higher symptom scores achieved a significantly greater improvement in symptom scores after operation than those with less severe symptoms, there was no correlation with the patient's perception of the outcome. In other words, the group with high symptom scores did not include a greater proportion of men with a successful outcome as determined by the patient's overall perception of success, though the numbers of men in each category were low.

Discussion

Measurement of the outcome of surgical interventions such as prostatectomy is not easy. For some men, this operation is performed for acute retention or chronic retention of urine and a successful outcome may be equated with satisfactory voiding and complete bladder emptying. On the other hand, for most men prostatectomy is performed with the intention of relieving symptoms: improvements in objective measurements such as flow rates and

Table 4 Mean Ranks of Scores and Probability of Observed Differences between Patients' Overall Assessment of Success of the Procedure
(Kruskall-Wallis one-way analysis of variance with ranks)

	Much better (n=23)	*Better (n=4)*	*Same (n=9)*	*Worse (n=3)*	*Probability Chi-squared adjusted for ties*
Post-op scores					
Patient: Irritative	14.59	22.38	29.94	28.50	0.003
Obstructive	16.22	26 75	21.94	34.17	0.013
Combined	14.30	25.13	27.11	35.50	0.001
Doctor: Irritative	14.76	26 25	28.44	26.50	0.006
Obstructive	16 13	26 63	24.67	26.83	0.066
Combined	14 74	27 00	28 33	26.00	0.006
Difference (Pre-operative—post-operative)					
Patient. Irritative	24 70	11.00	14 11	13 67	0.016
Obstructive	22.35	17.50	19 89	5 67	0.103
Combined	23 67	16 25	16.44	7 50	0.057
Doctor Irritative	22 59	10.25	17.72	20 00	0.205
Obstructive	23 15	17.25	16.00	11 50	0.182
Combined	23 52	11 00	16.89	14 33	0.100

residual urine may be reassuring but they do not necessarily mean that the patient has a good symptomatic outcome. Some method of standardising and quantifying these symptoms is, therefore, an essential part of measuring post-operative outcome.

Standardised questionnaires have been widely used in the assessment of symptoms associated with bladder outflow obstruction (Frimodt-Moller *et al.*, 1984). These are useful but require the involvement of a doctor. The concept of a self-administered questionnaire is an attractive one when it comes to audit and outcome measurement, for it allows patients to be assessed before and after operation without the direct involvement of a doctor. In addition, it removes a potential variable in that different doctors may place different interpretations on the questions. Such questionnaires have, however, shown that increasing symptoms of outflow obstruction occur with advancing age (Sommer *et al.*, 1990). Similar questions were used to study a series of 259 men undergoing prostatectomy (Fowler *et al.*, 1988). This study confirmed that about 80% of men were significantly improved by the procedure and that men with more severe symptoms had the better outcome.

The simple self-administered patient questionnaire showed a good degree of association with the traditional scoring system. Similar degrees of improvement in symptoms were shown using this questionnaire as were seen in a recent prospective study of prostatectomy (Neal *et al.*, 1989). One observed difference between the 2 questionnaires was that the scores relating to the strength and quality of the urinary stream were not closely associated. This is probably related to the rather subjective nature of the assessment in that the differences between a weak and dribbling urinary stream are not easy to define clearly. In addition, patients with detrusor instability who have frequency and low voided volumes often complain of a poor urinary stream because of low voided volumes.

Another difference was that, after operation, patients scored their irritative symptoms higher than did the doctors. As a consequence, the improvement in irritative symptoms observed by the patients, although significant, was not as great as that thought to be present by the doctor, suggesting perhaps that the patients' perception of the likely degree of improvement in these symptoms may have been unrealistically optimistic. It is a common impression that men endure a poor flow and consult their doctor only when urgency and nocturia appear. Failure of these symptoms to improve after operation is, therefore, likely to be viewed poorly by the patient. There is an obvious risk of over-estimating the degree of improvement in irritative symptoms after prostactectomy if the doctor's assessment alone is used.

Another strength of the self-administered questionnaire was that the patient's score correlated more closely with the patient's overall view of the outcome of the operation. The importance of the patient's perception of the risks and benefits of surgery is seen as being of increasing importance in the overall assessment of many surgical procedures (Wennberg, 1990). A successful outcome after operation was defined better by the absolute post-operative score than by the change in symptom score (pre-operative score minus post-operative score). The self-administered patient questionnaire was easy to administer and we suggest that it may prove useful, in conjunction with other instruments such as the Nottingham Health Profile (Hunt *et al.*, 1986), in assessing the outcome after operation in audit studies.

Appendix

Self-administered patient questionnaire

1) How long can you last between having to go to the toilet to pass water during the day?
More than three hours [ ] Two to three hours [ ]
One to two hours [ ] Less than one hour [ ]

2) How many times do you get up at night to pass water?
More than four times [ ] Two to three times [ ]
Two times [ ] Once or never [ ]

3) Do you ever wet the bed? Yes [ ] No [ ]

4) When you want to go to the toilet to pass water how long can you "hang on"?
As long as necessary—no problem [ ]
A long time, but have to look for a toilet [ ]
A short time (may have to rush to toilet or find a quiet place to pass water if no toilet available) [ ]
No time—you may have an accident [ ]

5) When you pass water, does the stream come out:
With a good flow, as strong as when you were younger [ ]
Sometimes bit weakly [ ] Always weak [ ] Only with a dribble [ ]
Dribbling always and stops + starts [ ]

6) When you want to go to the toilet to pass water, can you start:
Always straight away [ ] Sometimes have to wait [ ]

Always have to wait [ ] Have had occasional stoppages [ ]

7) After passing water, do you feel as if your bladder is empty?

yes [ ] sometimes not [ ] Usually not [ ]

8) When passing water do you have to strain to get the water out?

yes [ ] no [ ]

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A Simple Method for Insertion of an Intraprostatic Coil

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Summary—A simplified method of insertion of a urethral coil for treatment of benign prostatic obstruction has been tested in 25 patients.

The prostatic urethra is measured either by abdominal/transrectal ultrasound scanning or by rigid or flexible endoscopy. The coil is inserted into the prostatic urethra using simple measurements taken from a Foley catheter; 21 coils were correctly positioned at the first attempt using this new method—a success rate equivalent to that of ultrasound-guided insertion.

The urethral coil was introduced by Fabian in 1980 for the treatment of bladder outflow obstruction due to benign prostatic hypertrophy. Several reports have confirmed the value of the technique (Nordling *et al.*, 1989; Billiet *et al.*, 1990; Harrison and De Souza, 1990; Yachia *et al.*, 1990) as an alternative to surgery in patients who refuse prostatic surgery or are too unwell to undergo it.

The coil is inserted under topical urethral anaesthesia, in principle as an out-patient procedure. Until now, insertion of the stent has been guided by transabdominal ultrasound scanning (Nordling *et al.*, 1989; Billiet *et al.*, 1990) or by direct inspection using a rigid endoscope (Fabian, 1980; Harrison and De Souza, 1990). We have tested a new method of insertion of the urethral coil (Prostakath®) which can be used when ultrasound is not available.

Materials and Methods

The Prostakath is made in 7 lengths from 35 to 95 mm and comes with a specially designed insertion catheter. The steps in the new method of insertion are as follows.

1. The length of the prostatic urethra from the bladder neck to the external sphincter is measured. A Prostakath is selected which is 10 to 15 mm longer than the measured prostatic length.
2. A Foley catheter inserted into the urethra is gently drawn back until the balloon is resting against the bladder neck.
3. A mark is made on the catheter 15 cm from a fixed reference point at the sulcus between the pubic bone and the root of the penis (Fig. 1).
4. The balloon is deflated and the catheter removed so that the distance *K* between the balloon and the mark can be measured (Fig. 2).

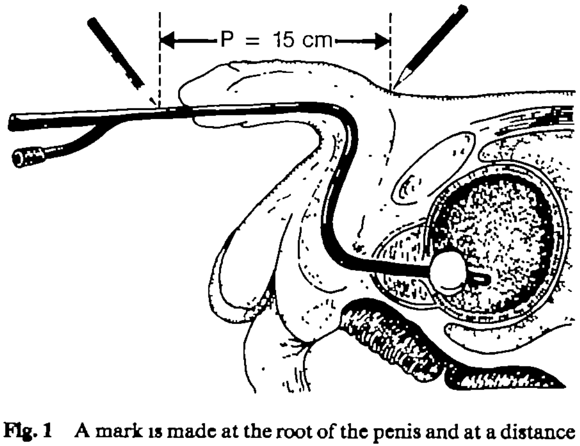

Fig. 1 A mark is made at the root of the penis and at a distance *P* = 15 cm on the catheter after the balloon has been gently positioned so as to rest on the bladder neck.

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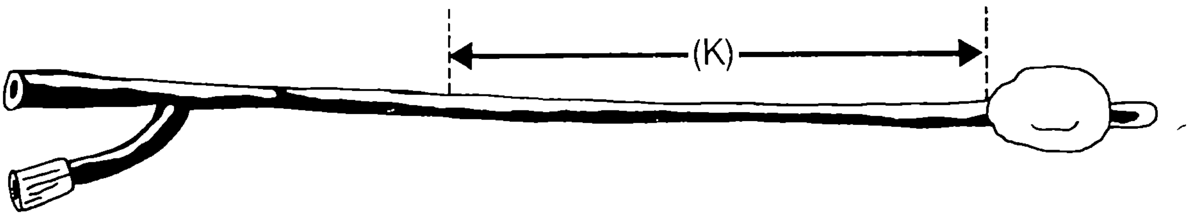

Fig. 2 Distance K is measured from the balloon to the mark on the Foley bag catheter.

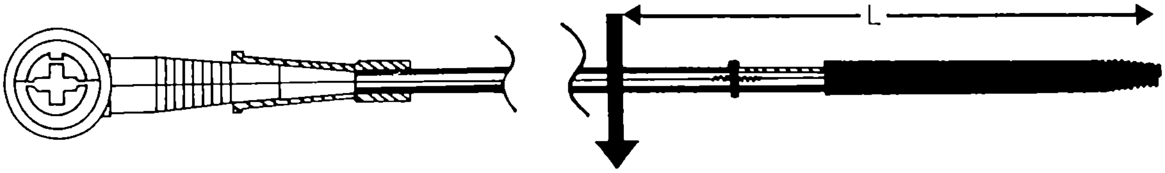

Fig. 3 Distance L is calculated as length of corpus of the coil subtracted from the prostatic urethral length and added to the distance K. During insertion the marker on the insertion catheter, as shown by the broad arrow, is placed at distance $P = 15$ cm from the mark on the root of the penis.

5. A mark is made on the Prostakath insertion catheter at a distance L from the tip of the coil, where L is given by the simple formula

   $L = K +$ (Prostakath length − prostatic length).
6. The Prostakath is then inserted using an F7 ureteric catheter as a guide as previously described (Nordling *et al.*, 1989) until the mark on the insertion catheter is 15 cm from the reference point at the root of the penis.
7. The position of the stent is checked by urethroscopy or ultrasound immediately after insertion and adjustments made where necessary.

Results

The Prostakath urethral coil was inserted using this method in 25 patients with bladder outflow obstruction due to benign prostatic disease. The median age was 77 years (range 62–94). The median prostatic urethral length was 4.8 cm (range 3.5–6.9).

Insertion of the coil was performed under topical urethral anaesthesia in all patients without complications. Urethroscopy or ultrasound after insertion revealed 21 coils correctly placed, 2 coils 1 cm too distal and 2 coils 1 cm too proximal. The distally placed coils were easily pushed into position and the proximal coils were re-sited with endoscopic forceps. All patients voided freely immediately after the Prostakath was correctly positioned, with a maximum flow rate of 8 to 38 ml/s (median 30.2). No patient was incontinent after the procedure.

Discussion

This method for insertion of the Prostakath is simple and was well received by the patients. It does not require ultrasound because the prostatic urethra can be measured during the flexible or rigid cystourethroscopy which we customarily perform to exclude bladder stones or tumours before the coil is inserted. We believe that the new method will allow more widespread application of this useful device.

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Encrustation of Intraprostatic Stents—a Comparative Study

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Summary—Metallic stents have been used in the management of prostatic disease in patients unfit for surgery. A variety of stents have become available but the optimum design and metal of construction has not yet been defined. This study examined one of the potential complications of stent insertion by demonstrating that they are susceptible to encrustation. Using an *in vitro* model it compares the ability of the different materials used in their construction to resist this encrustation. Titanium appears less able to resist deposition than the other metals examined. The long-term complication of encrustation may inhibit the use of some of these stents.

A plethora of treatment options have recently become available for the management of benign prostatic hyperplasia. Pharmacological therapy, prostatic stents and balloon dilatation, and more recently the use of microwave hyperthermia, are currently being evaluated for their safety and efficacy (Chisholm, 1989). The niche that each of these various treatment options is to occupy has yet to be clearly defined but it has been suggested that intraprostatic stents are most suitable for those patients unfit for surgery or who are awaiting surgery following acute retention (Nielsen *et al.*, 1990). A number of stents are currently available and consist of either expandable tubular mesh or removable metallic spirals. The expandable mesh stents are constructed of either titanium or a stainless steel super-alloy and are designed to allow epithelialisation over the surface. However, not infrequently, part of the stent is not completely covered and is consequently chronically exposed to urine. This has been found to occur in a significant proportion of patients (Chapple *et al.*, 1990), usually where the stent protrudes into the bladder from the prostatic urethra. The metallic spiral stents are not designed to be covered by epithelium and are in constant contact with urine, but are able to be removed with relative ease. The earlier spiral stents were made of stainless steel, but others have subsequently been covered with a layer of gold in an attempt to inhibit the formation of encrustations. The exposure of any of these metals to urine subjects them to the risk of encrustation and stone formation. The appearance of stones on metal staples used in urinary reconstruction is a common phenomenon (Skinner *et al.*, 1984) and it seems probable that they will also appear on metallic stents where there is an interface between metal and urine.

This study aimed to analyse prostatic stents and to establish their ability to resist encrustation. A variety of stents that were removed from patients were analysed for encrustations. Stents were also tested in an encrustation model to try to identify which of the various types of metal in prostatic stent construction is most suitable for long-term exposure to urine in terms of encrustation resistance. All prostatic stents will have their surface exposed for a period until epithelisation occurs, and if epithelialisation is incomplete part of the surface will be permanently exposed.

Materials and Methods

Four titanium mesh stents and 1 stainless steel Porges spiral stent were removed from patients at intervals of 1 week to 3 months after insertion. We looked for infection in the urine at the time of stent introduction and removal. The stents were examined by scanning electron microscopy (SEM) and infra-red spectroscopy (IRS) for evidence of encrustation deposition and its composition.

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Four different types of stent were then placed in an encrustation model, to assess the susceptibility of each metal to encrustation deposition. The stents examined were:

(1) Titanium mesh stent (ASI)
(2) Stainless steel super-alloy mesh stent (AMS)
(3) Stainless steel alloy spiral (Porges)
(4) Gold-plated spiral (Prostakath).

The metals were each examined before and after exposure to the encrustation model, by a combination of SEM and IRS. The stents were fashioned, prior to urine exposure, to weigh approximately the same so that a comparative weight change could be obtained. This could not be done for the gold-plated stent, which was heavier than the others. The stent samples were weighed prior to and after exposure so that a quantitative as well as qualitative evaluation of the encrustations could be made. This enabled a direct comparison to be made between the types of metal. The encrustation model involved flowing sterile urine over the intact stent in a self-contained "flow-cell", in which the urine circulated at a constant speed of 1.5 ml/min via a peristaltic pump. The urine was maintained at 37°C and the sterility confirmed by serial microscopy and culture. The pH was measured with a standard pH meter, and the urinary constituents were maintained by complete replacement of the urine, obtained from a single source (S.A.V.H.), every 24 h. Each stent was examined in the flow-cell for a period of 14 days.

Results

The stents removed from patients revealed encrustations on 2 of the 5 examined. The stainless steel alloy spiral stent was obstructed by encrustations that were composed of magnesium ammonium phosphate (struvite). The urine of this patient was found to be infected with a *Proteus* species at the time of removal, which had not been present at the time of insertion. The titanium stents all showed signs of epithelial overgrowth; 1 showed evidence of exposure to urine, and encrustations had formed on the surface of the metal.

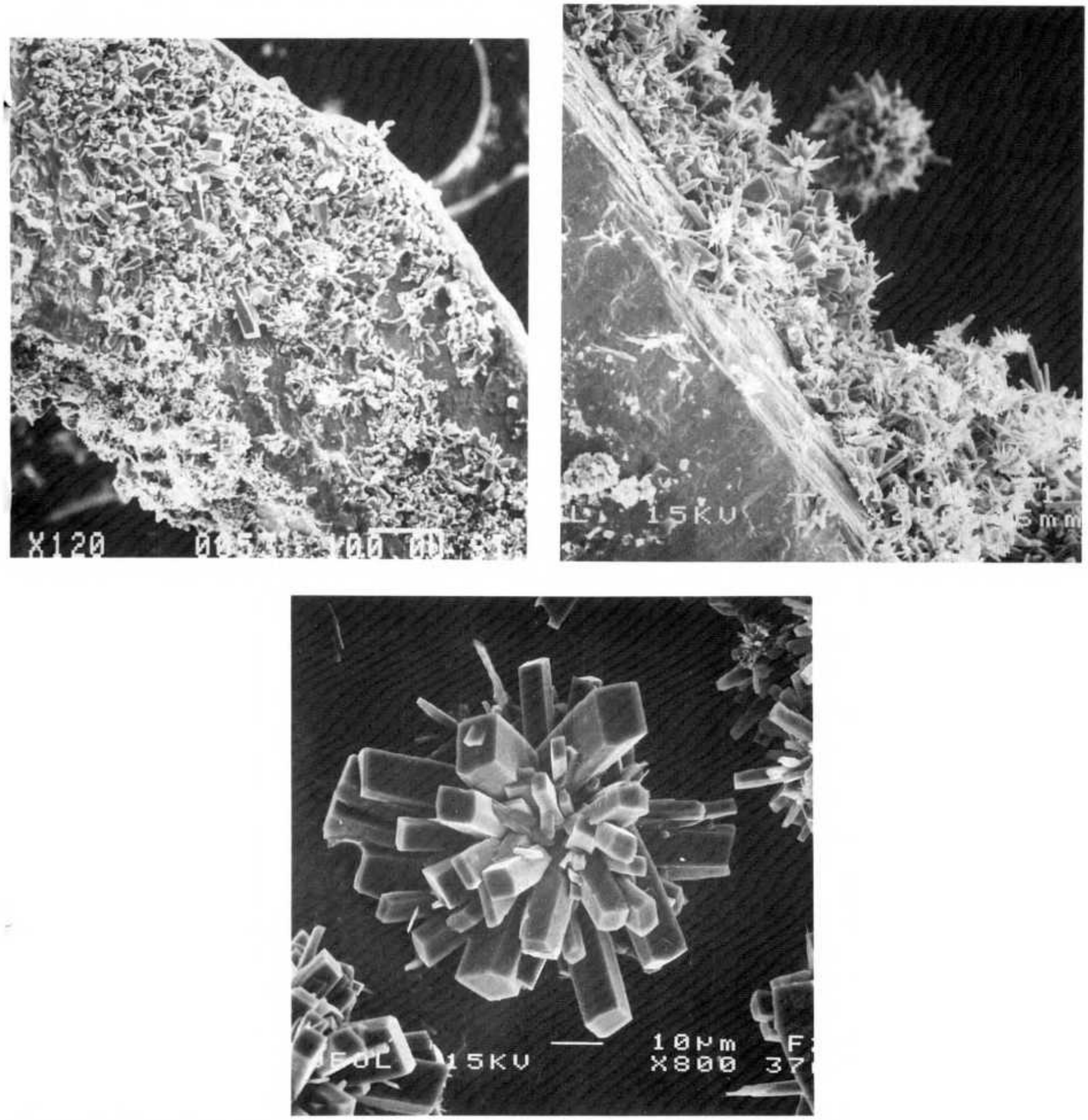
The *in vitro* study on 4 types of stent showed that encrustations were able to form on all of those examined after 14 days' exposure to urine. The titanium stent allowed the greatest deposition, with a 0.9% increase in dry weight. This is demonstrated by SEM (Figs 1–3), which reveals the deposition of calcium phosphate crystals as brushite on the stent surface. The stainless steel alloy and gold-plated stents also developed encrustations, as demonstrated by SEM (Fig. 4), but to a lesser degree (Table).

Discussion

The introduction of foreign bodies into the urinary tract has long been associated with the problems of infection and encrustation. Prosthesis infection often occurs in the form of a biofilm, with bacteria adherent to the polymer surface within a polysaccharide matrix, making the organisms resistant to the effects of antibiotics. Encrustations are able to form in the presence of either infected or sterile urine, though the mechanism of each is different. In infected urine, urease-producing organisms cause the hydrolysis of urea, and the subsequent elevation of pH in which magnesium ammonium phosphate (struvite) is precipitated. The rapid deposition of this stone is demonstrated by the spiral stent that was removed from the patient with a *Proteus* urinary infection. Stone was deposited on the intravesical portion of the stent and within the lumen, leading to obstruction (Holmes and Kirby, 1992).

The formation of encrustations in sterile urine appears to be dependent on both the urinary constituents and the properties of the synthetic material. Encrustations have been shown to occur more readily in known stone formers (Ramsay *et al.*, 1987) and the chemical composition and surface characteristics of polymer materials may also influence their formation. Most of the previous work on encrustation has been performed on polymer materials used in urethral catheter manufacture, and favourable characteristics include chemical inertness, surface smoothness and features of hydrophilicity (Cox *et al.*, 1988; Cox, 1990). These features are more easily achieved with complex polymer design and construction than with currently available metal materials. However, a polymer that resists encrustation is not currently available and if metal materials are to be used in the urinary tract, attention should be drawn to their comparative susceptibility to encrustation.

The expandable mesh stents must epithelialise completely if the problem of encrustation is to be avoided. This has been difficult to achieve becuse of the problem of accurate stent positioning. Insertion is performed by direct urethral measurement, under fluoroscopic control (McLoughlin *et al.*, 1990), trans-rectal ultrasound control and more recently under direct vision. During insertion of the ASI stent, compensation for stent length reduction



Figs 1–3 Crystal deposition on titanium stent at increasing magnification.

Table

Stent material	*Weight (g)*		Percentage change
	Before	*After*	
Titanium (mesh)	0.416	0.4241	0.92
Steel super-alloy (mesh)	0.4095	0.409	−0.12
Steel (spiral)	0.4394	0.442	0.59
Gold-plated (spiral)	2.0006	2.0021	0.075

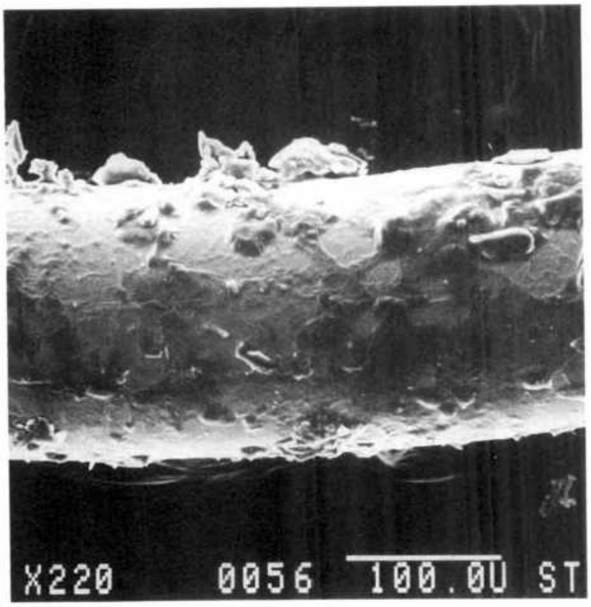


Fig. 4 Steel alloy stent showing less deposition than on titanium.

during expansion must be taken into account, making accurate placement more difficult. Stent protrusion into the bladder also occurs with the AMS stent (Chapple *et al.*, 1990) with exposure of metal to urine. Even if the stent is of the correct length the non-cylindrical configuration of the prostatic urethra may result in areas of the stent which are not in close apposition with epithelium and are therefore unlikely to be fully covered, even in the long term. Our *in vitro* studies show that the titanium stent has the greater amount of encrustation, as demonstrated by the surface appearance and the measured weight gain, compared with the stainless steel. The titanium surface is less smooth (Fig. 5) than the stainless steel and may account for this difference.

The problem of encrustation is one of the complications of expandable mesh stent insertion and is a feature of the influence that the stent material has on the urine. Similarly, urine and other body fluids are potentially able to exert a deleterious effect on the stent by the action of surface corrosion. The corrosive nature of the saline component of body fluids makes long-term implantation of metals potentially hazardous. Implant metals rely on the formation of a passive metal oxide film on their surface for their corrosion resistance. If this film is damaged metal ions are released, with a subsequent foreign body inflammatory reaction and a risk of tumour development (Sunderman, 1989). Studies have been performed on a variety of metals,

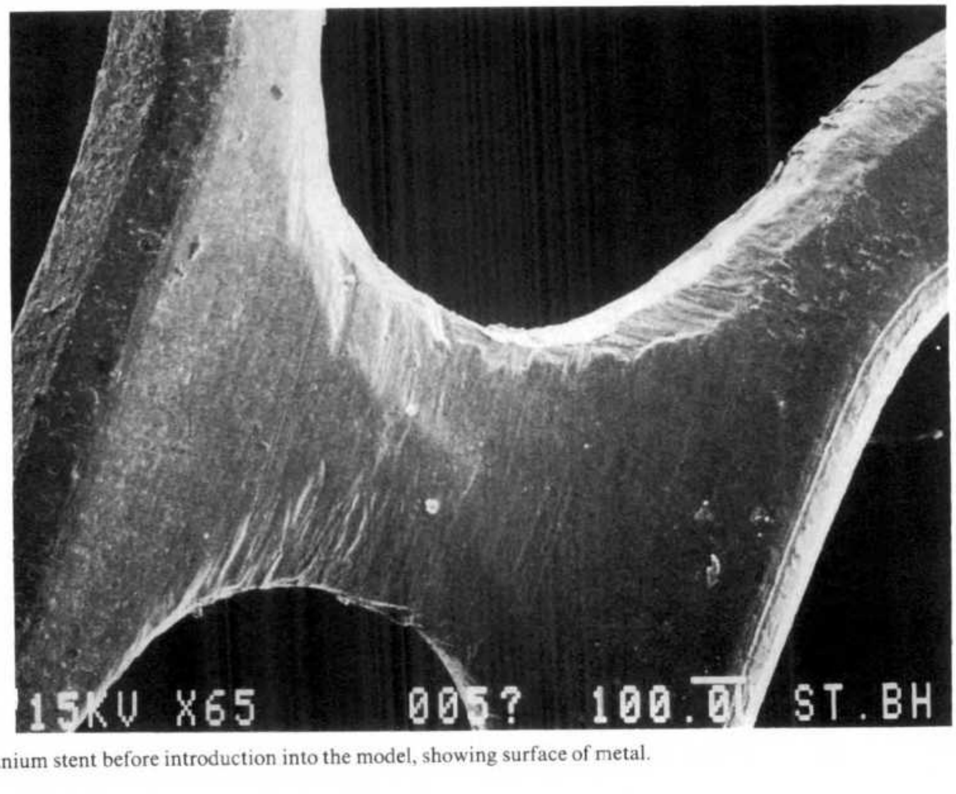


Fig. 5 Titanium stent before introduction into the model, showing surface of metal.

including titanium (Williams, 1981) and medical grade stainless steel (Harris, 1979), to compare their corrosion resistance and susceptibility to stress corrosion cracking under conditions of mechanical stress. Titanium appeared to be superior to stainless steel in terms of corrosion resistance where stresses were only moderate, and thus more suitable for long-term implantation.

Both removable spiral stents resisted encrustation comparatively well. The stainless steel alloy and the gold-plated spiral stent, which is constructed with a 99% gold and 1% silver coating, appeared to be appoximately equally resistant to encrustation in sterile urine in terms of weight gain, though a longer period of exposure may reveal differences. The long-term use of these stents in the prostatic urethra should probably be avoided and when *in situ*, urinary infection should be scrupulously prevented so as to avoid encrustation and obstruction. These stents can, however, be removed and replaced more easily than the expandable mesh stents, whose removal is often difficult, especially when they have been *in situ* for some time and the presence of encrustations first becomes apparent.

The role of intraprostatic stents in the management of benign prostatic disease has yet to be clearly established. Certainly the ideal type of metal used for construction has not been defined, though we propose that the smooth surface of the extruded metals may confer some resistance to encrustation. Consideration may also need to be given to the potential hazard of metal corrosion if the stent is to remain *in situ* for long periods, which may favour use of the titanium stent. The full clinical significance of both encrustation formation and corrosion is currently unknown since clinical results of long-term insertion are unknown. When using the expandable mesh stents every effort should be made to prevent exposure of the metal surface to urine. When using any prostatic stent, urinary infection should be assiduously sought and rigorously eradicated because encrustations form rapidly on foreign bodies in infected urine.

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Dynamic Clearance: Mathematical Assessment of Flow Mechanics in Prostatic Resection

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Summary—The understanding of flow mechanics in endoscopy is poor. In prostatic surgery, emphasis has been placed on limiting the rise of intravesical pressure with little regard to the effect on flow mechanics and visibility. A model has been developed using dynamic clearance to compare different methods of prostatic resection. The results show that in a 0.95-cm glass urethra, continuous flow irrigation has slower clearance at all flow rates when compared with intermittent irrigation and suprapubic suction. Although intravesical pressure is important, attention should also be paid to flow dynamics and more emphasis should be placed on this when new instruments and fluid delivery systems are developed.

Improvements in instrument design and optics have greatly facilitated endoscopic surgery, but fluid delivery systems have remained unchanged for many years. The problems of prostatic surgery and irrigating fluids are particularly important. The continuous flow resectoscope was introduced by Iglesias *et al.* (1975) to reduce peri-operative fluid absorption by keeping intravesical pressure low. The suprapubic shunt is also operated under the same principles (Madsen and Frimodt-Moller, 1984). No objective tests have been performed to assess the influence of flow mechanics in endoscopic surgery. The aim of the irrigating fluid is principally to allow vision down the instrument by keeping the lens and immediate vicinity clear of blood and debris.

We have devised the dynamic clearance test, by which we can assess the effect of different irrigating methods on visibility and clearance of blood from the operating field of a resectoscope.

Materials and Methods

A moulded glass tube (urethra), 0.95 cm in internal diameter, was connected to a moulded glass reservoir (1L bladder), which was open to the atmosphere. Into the glass urethra a 26 F gauge genitourinary continuous flow resectoscope was introduced. The loop of the resectoscope was 1 cm from the end of the urethra. From the bladder end of the urethra a needle was introduced which lay just underneath the resectoscope loop. Small boluses of dye could then be injected into the area between the loop in its most distal position and the resectoscope, an area known as the working area of the resectoscope. The time course of the way in which this dye was washed out from the working area was determined.

To measure the clearance of the dye a light source and a silicon photodiode with integrated amplifier were placed across the glass urethra (Fig. 1). The light source emitted at 635 nm. The active sensitive area of the photodiode was 5 mm^2. The light path was placed to observe the area just proximal to the loop of the resectoscope, *i.e.* the working area. On injection of the dye into the working area the photo cell would record a drop in voltage which would return to baseline as the dye was removed from this area. The read-out was recorded on a chart recorder.

Continuous flow irrigation and suprapubic suction irrigation (input and output were equal) were compared with intermittent irrigation (inflowing fluid only). All systems were gravity fed from a

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constant overflow tank (height 80 cm). A centrifugal pump achieved output in the continuous flow irrigation and suprapubic suction irrigation. Each system was compared at 5 flow rates: 14.5, 11.7, 9.7, 7.5 and 5 ml/s. These flow rates were achieved by using rotameters on inflow and outflow tubing.

For each method at each flow rate the test was repeated 5 times. From the point of maximum darkness (lowest voltage), which was time = 0, the height of the washout curve was measured at constant time intervals.

These results were then normalised and the natural log found. The natural log of the normalised values when plotted against time will result in a straight line for an exponential washout curve. The reciprocal of the gradient of this line will be a time constant T. For each method of each flow rate the grouped data were examined. The gradients and time constants of continuous irrigation, suprapubic suction and intermittent irrigation in a 0.95-cm urethra are shown in the Table.

Results

The gradients, their standard error and the time constants for the 3 methods are shown in the Table. The gradients with standard error bars are shown graphically in Figure 1. It can be seen that intermittent irrigation and suprapubic suction gave similar results but the results of continuous flow were notably different. With increasing flow rates, as expected, the gradients became larger (quicker washout time) in all methods of irrigation. In

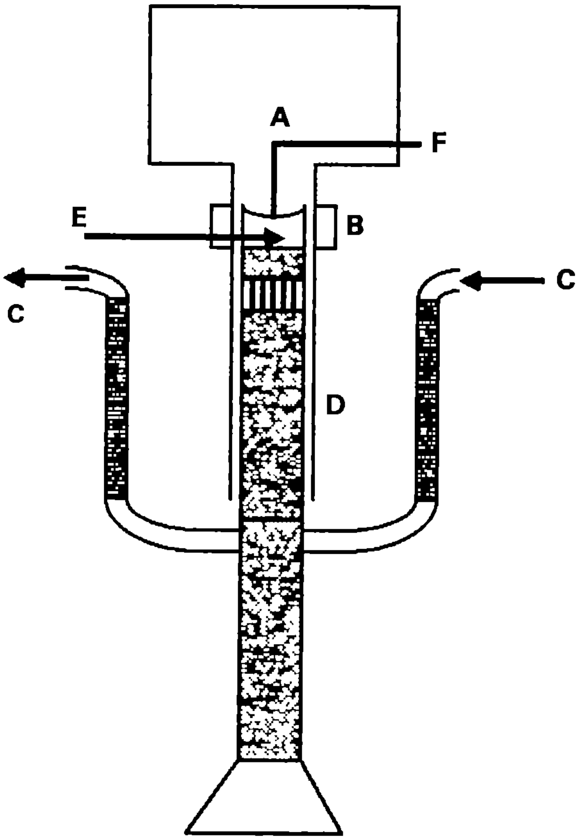

Fig. 1 Experimental model used for dynamic clearance test. A. bladder B· photo cell. C· fluid inflow and outflow via rotameters D: resectoscope. E· working area of resectoscope. F. dye injection needle.

Table Gradient of Grouped Results with Standard Errors for each Method of Irrigation and at each Flow Rate. (Time constant for each gradient is also shown)

Flow rate (ml/s)	*Continuous irrigation* G	T	*Suprapubic suction* G	T	*Intermittent irrigation* G	T
14.5 SE	−1.67 ±0.107	0.59	−4.69 ±0.15	0.21	−3.86 ±0.37	0.26
11.7 SE	−1.13 ±0.098	0.88	−3.42 ±0.22	0.29	−3.55 ±0.17	0.28
9.7 SE	−0.91 ±0.038	1.1	−2.14 ±0.11	0.46	−2.38 ±0.091	0.42
7.5 SE	−0.89 ±0.63	1.12	−1.96 ±0.87	0.51	−1.77 ±0.06	0.56
5.0 SE	−0.63 ±0.025	1.59	−1.14 ±0.037	0.87	−1.17 ±0.041	0.85

G = Gradient. T = Time constant (reciprocal of the gradient). SE = Standard error.

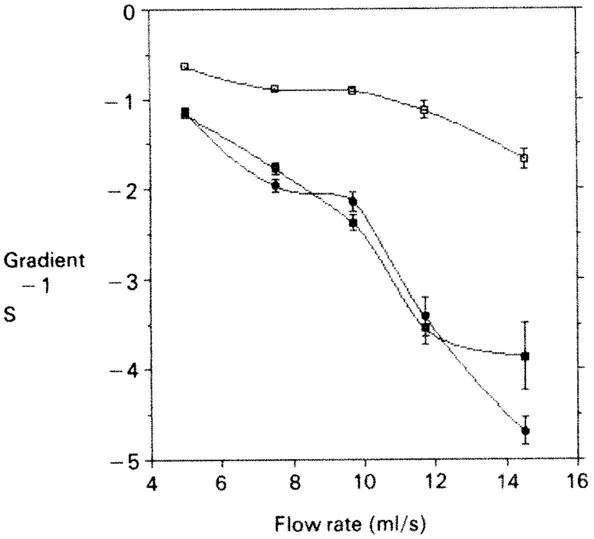

Fig. 2 Gradients and standard errors of 3 methods of irrigation at different flow rates. □: continuous flow irrigation. ●: suprapubic suction irrigation. ■: intermittent irrigation.

continuous flow these gradients were noticeably slower than in the other types of irrigation. In the confined environment of the model urethra, continuous flow irrigation caused the longest washout times and thus the worst visibility.

Discussion

The pressure that develops in the prostatic fossa has been linked to absorption of irrigating fluid during transurethral prostatectomy (Madsen and Naber, 1973). Methods to reduce prostatic fossa and bladder pressure during resection were introduced and consisted of a continuous irrigating resectoscope with inflow and outflow channels (Iglesias *et al.*, 1975). Widran (1985) introduced a balanced pumping system with a built-in pressure monitor to keep control of the intravesical pressure. Continuous flow has been shown to reduce resection time in some studies (Mackenzie, 1978), but others have shown no difference in resection rates (Stephenson *et al.*, 1980; Flechner and Williams, 1982). If continuous flow resectoscopes do dispense with the need to stop the operation frequently to empty the bladder, the resecting time should be much quicker. It may be that continuous irrigation adversely affects the fluid jet, so that vision is reduced. Our model has shown that there are differences in the different methods of resection and that although continuous irrigation may keep bladder pressure low, visibility is adversely affected.

The results obtained with the suprapubic drainage and intermittent irrigation methods are very similar, implying that removal of the irrigating fluid from the bladder does not adversely affect the fluid jet in the urethra. When the irrigating fluid is removed via a continuous flow resectoscope, and inflow and outflow are balanced, the effective fluid jet must be reduced, leading to smaller gradients and longer washout times. In the clinical situation this will mean poor visibility for the operator.

Suprapubic drainage via a shunt (Adair, 1972) with low pressure irrigation has also been shown to keep bladder pressure low (Reuter and Jones, 1974). Suprapubic drainage results in better clearance than continuous flow irrigation but is more invasive in the clinical setting.

Although a glass model with its obvious limitations has been used in this study, it enables mathematical and computer modelling for the design of endoscopic equipment. For the first time accurate parameters can be defined which will lead to objective assessment of the optimal endoscopic and fluid pumping design for endoscopy.

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Circulating Prostate Specific Antigen-positive Cells Correlate with Metastatic Prostate Cancer

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Summary—Analytical flow cytometry was used to study circulating prostate specific antigen (PSA)-positive cells in 40 consecutive patients with newly diagnosed, untreated prostate cancer; 25 patients (63%) had metastatic disease confirmed by a positive bone scan. Cell suspensions were prepared for each patient from both the primary tumour and peripheral blood samples. The cells were stained with a monoclonal antibody against PSA, and analysed by flow cytometry; PSA-positive cells were sorted according to their immunofluorescence and light scatter properties. The cellular deoxyribonucleic acid (DNA) content of each specimen was also analysed to establish ploidy status. PSA-positive cells were detected in the peripheral blood of 33 patients (83%). The presence of these cells in the circulation showed a higher degree of sensitivity and specificity in predicting positive bone scans than did serum PSA levels. Circulating PSA-positive cells may represent either a subpopulation of tumour cells with distinct metastatic properties or, alternatively, host immunocytes which take up PSA in an active or passive manner.

The development of metastases is one of the most significant events in the natural history of cancer. It is a complex, multisequential phenomenon occurring by the dissemination of malignant cells from the primary tumour. Animal studies have shown that tumour metastasis is not simply a random event and it is now well established that a malignant tumour consists of subpopulations of cells which differ in their metastatic capacity (Poste and Fidler, 1980). Cells with specific invasive properties must therefore disseminate via the blood or lymphatics and survive, before secondary disease can be established (Fidler and Kripke, 1977). To date, it has been difficult to study the release of tumour cells into the circulation, in part because of their limited survival in the blood stream (Fidler, 1970).

Prostate cancer is the third most common malignancy in men in England and Wales, with 9513 new cases registered in 1985 (Office of Population Censuses and Surveys, 1985). Approximately 50% of patients present with metastatic disease and have a poor prognosis, with a median survival of less than 3 years (Whitmore, 1984). By contrast, in those patients with localised disease which fails to progress beyond the confines of the gland, a 5-year survival rate of up to 93% can be expected (George, 1988; Johansson *et al.*, 1989). In addition, autopsy studies have shown that many men over the age of 80 harbour a prostatic cancer which never becomes clinically manifest (Hirst and Bergman, 1954). This unpredictable behaviour of prostate cancer may be explained by the cellular heterogeneity of each individual tumour, and disease progression by subtle changes at cellular, genetic and molecular levels.

Attempts have been made to predict the biological behaviour of prostate cancer. While tumour stage and volume, serum prostatic specific antigen levels, histopathological grading and DNA tumour ploidy status have all been shown to correlate with prognosis and survival (Tavares *et al.*, 1973; deVere

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Read at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

White and Deitch, 1989; Gittes, 1991), none of these methods can predict reliably those tumours which are likely to progress and metastasise.

The need for new criteria to define the invasive and metastatic potential of individual cases of prostate cancer is increasing, particularly in view of the recent trend towards more aggressive treatment of this common malignancy. In the present study, we have used flow cytometry in an attempt to detect circulating tumour cells in patients with both local and metastatic prostatic carcinoma. The clinical significance and possible nature of these cells are discussed.

Patients and Methods

Forty patients with newly diagnosed, untreated prostate cancer were studied. Their ages ranged from 49 to 85 years (median 72). Confirmation of the diagnosis was based on digital rectal examination, 3 serial serum PSA measurements (immunometric radioimmunoassay, CIS, UK) and transrectal prostatic biopsy. All patients had a full blood count and a technetium 99m bone scan before the start of the study.

A summary of the methods is shown in Figure 1. Peripheral blood samples (5–10 ml in EDTA) were collected prior to prostatic manipulation. Primary tumour tissue was obtained either from needle core biopsies or from prostatic transurethral resection specimens. The presence of carcinoma was confirmed using standard histological criteria.

Cell suspensions were prepared from solid tumours by mincing the specimens with crossed scalpels, filtration and mechanical dissociation in phosphate buffered saline. Density gradient separation with lymphocyte separating medium (J-Prep. TechGen. International Ltd, London, UK) was used to obtain cell suspensions from peripheral blood samples. The cell suspensions were divided up for DNA analysis and monoclonal antibody (MoAb) staining. DNA ploidy status was measured using the fluorochrome propidium iodide (DNA CycleTest, Becton-Dickinson UK Ltd); MoAb staining was performed both by a direct (fluorescein isothyocyanate or FITC conjugated primary MoAb) and an indirect 2-stage technique (primary MoAb followed by FITC goat anti-mouse f(ab′)2 antibody; Caltag, Bradsure Biologicals Ltd, Leicestershire, UK). Each MoAb assay included a negative control (isotype or F(ab′)2 only), a positive control MoAb against the leucocyte common antigen (CD45RB LCA, Dako UK Ltd) and a prostate cell MoAb against prostate specific antigen (PSA Dako UK Ltd). All MoAb stained cells were maintained at 4°C and analysed fresh by flow cytometry.

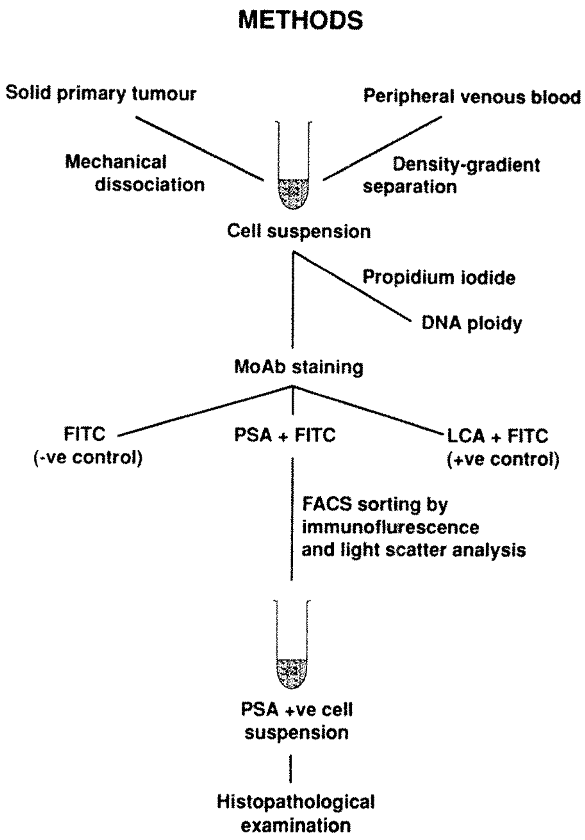

Fig. 1 Summary of methods. DNA: deoxyribonucleic acid. MoAb: monoclonal antibodies. FITC: fluorescein isothyocyanate. PSA: prostate specific antigen. LCA: leucocyte common antigen. FACS: fluorescein activated cell sorter.

A control group of 15 males with known benign prostatic hyperplasia (BPH), undergoing transurethral resection, had their prostatic tissue and peripheral blood analysed in a similar fashion. Peripheral blood analysis was also carried out on 5 healthy females.

The DNA content was measured on at least 10,000 cells from each sample of one million cells and MoAb positivity was assessed in a similar representative sample. MoAb binding was expressed as a percentage of the whole sample for 2 reasons: firstly, to allow comparison of data between patients and, secondly, to enable simultaneous analysis of both MoAb staining and light scatter properties. Absolute cell numbers were not considered to be accurate owing to difficulties in quantifying abnormal cells on routine blood analysis.

Two flow cytometers were used; a Becton-Dickinson FACS 420 with accessory Consort 30 computer on which cells were sorted, and an Ortho Diagnostic Orthocyte for DNA analysis. Cells were stained after sorting with Papanicolaou and haematoxylin and eosin stains for cytological examination. Representative samples were selected and examined by electron microscopy.

The data are reported as medians, ranges and 95% confidence intervals. Non-parametric statistical analysis was performed using the Mann-Whitney U test.

The study was approved by the Ethical Committee and informed consent was obtained from all patients.

Results

Technetium 99m isotope bone scans showed increased uptake in 25/40 patients (63%), confirming the presence of skeletal metastases. Full blood counts were all within normal limits. DNA ploidy of primary tumours and cell suspensions, measured by flow cytometry, showed that 24 patients (60%) had a diploid primary tumour, with 17 of them having detectable levels of diploid circulating PSA-positive cells. The remaining 16 patients (40%) had an aneuploid primary tumour, with 15 of them having circulating diploid PSA-positive cells, and only 1 patient showing aneuploid cells in the peripheral blood. In each prostate tumour sample a median of 68% (range 32–92%) of cells were PSA-positive, while a median of only 6% (range 0–54%) of cells in peripheral blood buffy layers stained positive for PSA.

Circulating PSA-positive cells were detected in all 25 patients with a positive bone scan, at a median rate of 16% (range 2–54%) staining positive in each cell suspension; 23 of these patients had serum PSA levels >4 μg/l (median 72 μg/l, range 1–120). By contrast, only 7/15 patients with a negative bone scan had circulating PSA-positive cells, and then in only a small percentage of cells (median 1%, range 1–6); 12 of these 15 patients had serum PSA levels >4 μg/l (median 17 μg/l, range 1–120) (Fig. 2). This difference in the percentage of PSA-positive cells between bone scan positive and bone scan negative patients was highly significant ($P<0.00001$). The presence of more than 2% of circulating cells staining positively for PSA showed a greater sensitivity (96%) and specificity (60%) in detecting skeletal metastases then did serum PSA levels at cut-off values of 4 μg/l (sensitivity 92%, specificity 20%) or 20 μg/l (sensitivity 76%, specificity 53 5%). A summary of the results is shown in Tables 1 and 2.

None of the patients in the control groups had PSA-positive cells in their peripheral blood. Four male patients with BPH and enlarged glands (over 50 g resected) had pre-operative serum PSA levels >4 μg/l (median 7 μg/l, range 4–15). PSA-positive cells were found in every BPH tissue sample, with a median of 56% (range 38–85%) of each cell suspension. These cells were all diploid on DNA analysis.

Cytologically, although PSA-positive cells were

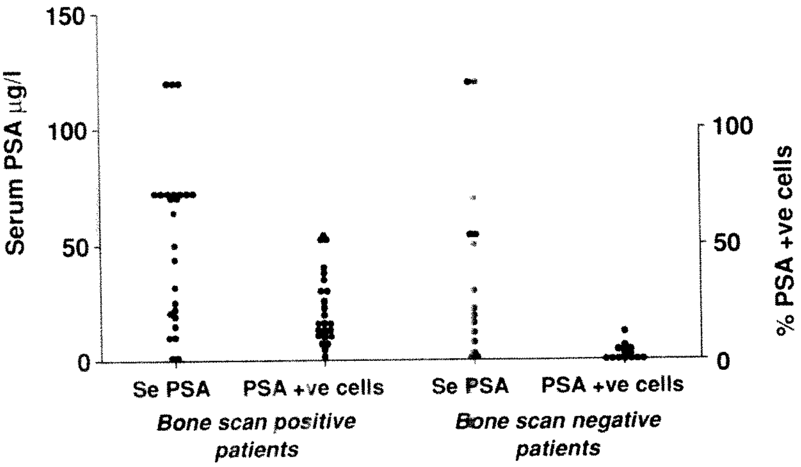

Fig. 2 Serum PSA values versus percentages of PSA-positive cells in the peripheral blood of patients with a positive (n = 25) and a negative (n = 15) bone scan.

Table 1 Serum PSA Versus Circulating PSA-Positive Cells in Patients with Positive (n = 25) and Negative (n = 15) Bone Scans

Bone scan	*Serum PSA (µg/l) Median (95% confidence interval)*	*PSA-positive cells (%) Median (95% confidence interval)*
Positive	72 (42–73)	16 (15–28)
Negative	17 (9–46)	1 (1–3)
	$P<0.01$	$P<0.00001$

large, with multiple nucleoli and slightly clumped chromatin at light microscopy level, it was difficult to distinguish between the morphology of these putative prostatic carcinoma cells and cells of monocyte/macrophage lineage. Furthermore, preliminary electron microscopy on representative samples of sorted PSA-positive cells failed to demonstrate features suggesting an epithelial origin. The nature of PSA-positive cells is therefore controversial and remains to be determined. PSA-negative cells consisted mainly of lymphocytes, monocytes and polymorphonuclear leucocytes.

Discussion

Bony metastases are a major cause of morbidity in patients with prostate cancer (Whitmore, 1984). Technetium 99m isotope bone scanning is currently the most reliable method for the detection of skeletal metastases. However, serum PSA levels at a cut-off value of 20 ng/ml were found to be the best predictor of bone scan findings in a recent comparison of tumour grade, local clinical stage, serum PSA and acid phosphatase (Chybowski *et al.*, 1991). The results of the present study do not contradict this view, but a considerable overlap in serum PSA values in patients with positive and negative bone scans was observed.

We have used tissue specific MoAb staining and flow cytometry to detect and sort circulating PSA-positive cells in prostate cancer patients. Assessment of DNA content was also performed on tissue and circulating cells. With the exception of 1 patient, all circulating cells, whether PSA-positive or negative, were diploid. By contrast, 40% of primary tumours had aneuploid cell populations, which may not have been detected in the blood stream because of the relatively small numbers of cells analysed. Alternatively, diploid tumour cell populations may constitute the majority of escaping cells.

From the results presented, PSA-positive cells do not appear to be released in the circulation at detectable levels in BPH, or in patients with raised serum PSA levels and a large benign prostate gland. This suggests that the shedding and survival of PSA-positive cells into the blood is related to the presence of carcinoma, proving to be a more reliable indicator of metastatic disease than serum PSA concentrations. Both the sensitivity and specificity in predicting skeletal metastases were greater with increased percentages of PSA-positive cells than elevated serum PSA. It is likely that both local extracapsular extension and systemic metastases are responsible for high serum PSA levels, whilst PSA-positive cells in the circulation are a more specific indicator of disseminating disease. Alternatively, PSA-positive cells may not be of malignant origin, but could represent normal host cells of the immune system. The cells may passively express PSA, either as a result of its association with external membrane determinants or through being taken up by the cells, processed and re-expressed as an integral membrane component. This latter function, which may be referred to as antigen processing and presentation, is a property of mononuclear phagocytes, B-lymphocytes and, in a more restricted manner, natural killer-large granular lymphocytes (Unanue, 1984; Brooks and Moore, 1986; Roncarolo *et al.*, 1991). The definitive explanation for the results given here has still to be determined. Furthermore, the modulatory effect of PSA on immune function has to be investigated.

Finally, although some cytological features of

Table 2 Serum PSA Versus Circulating PSA-Positive Cells in Predicting Bone Scan Findings

	Sensitivity (%)	*Specificity (%)*	*Predictive value (%)*	*False +ve (%)*	*False −ve (%)*
Serum PSA (µg/l)					
Cut-off level 4 µg/l	92	20	66	34	40
Cut-off level 20 µg/l	76	54	73	24	42
%PSA-positive cells					
Cut-off level 2%	96	60	80	20	1

PSA-positive cells suggested a malignant origin, electron microscopy has not confirmed that fact. These cells may represent a "subpopulation" of tumour cells with metastatic potential, but this remains to be established. The techniques described will, however, allow the isolation and further characterisation of these cells. Such studies may, in future, identify a group of patients with prostate cancer whose tumours carry definite metastatic potential. This would enable aggressive surgical treatment to be directed at those most at risk of dying from this common malignancy.

Acknowledgements

We are grateful to Mr J. B. F. Grant for allowing us to study his patients. The study was funded by the Special Trustees for the Former United Sheffield Hospitals. Flow cytometry at the University of Sheffield Medical School is supported by the Yorkshire Cancer Research Campaign.

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Sphincter Electromyography in Patients after Radical Prostatectomy and Cystoprostatectomy

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Summary—Urethral sphincter weakness may occur after major pelvic surgery and urinary incontinence, either temporary or permanent, may result. In order to determine whether the cavernous nerves described by Donker and Walsh carry fibres to the distal urethral sphincter as well as those supplying the corporal bodies, we have studied prospectively the sphincter electromyography in 2 groups of 10 patients: (1) those who had undergone nerve-sparing radical prostatectomy for prostatic carcinoma and (2) those who has undergone radical cystoprostatectomy for bladder carcinoma. This study group was compared with a control group of normal individuals. The results showed significant differences in duration of motor units between the control group and prostatectomy group and between the control group and cystectomy group but no significant difference between the 2 operated groups. There was no significant difference in amplitude of the motor units, the sacral reflex latencies or the pudendal somatosensory evoked potentials between all 3 groups. It was therefore concluded that division of the cavernous nerve of Walsh does not compromise distal urethral sphincter function. Furthermore, radical transabdominal lower urinary tract surgery may induce significant electromyographic changes in the external sphincter which may not be clinically evident. This may potentially affect continence later if second-stage urinary reconstructive surgery is undertaken.

Since the documentation of the anatomy of the cavernous nerves and their innervation of the corporal bodies by Walsh and Donker (1982), nerve-sparing radical lower urinary tract surgery such as radical prostatectomy has become more popular and may preserve potency. However, the functional relationship between these nerves and the distal urethral sphincter is less certain, although their close anatomical association is well established.

Various degress of sphincter weakness may occur after major pelvic surgery, whether colonic, gynaecological or urological. As a result, temporary or permanent urinary incontinence may occur.

Since the introduction of clinical electromyographic (EMG) examination of the urethral sphincter (Franksson and Petersen, 1953), urethral sphincter EMG analysis has become established in the investigation of various disorders of continence and potency as well as other neurological diseases. The aims of this study were to determine whether the cavernous nerves carried fibres to the distal sphincter as well as those supplying the corporal bodies, and whether EMG changes occurred after radical lower urinary tract surgery.

Patients and Methods

We studied prospectively the sphincter electromyography in 2 groups of patients: (1) those who had had nerve-sparing radical prostatectomy for prostatic carcinoma and (2) those treated by radical cystoprostatectomy for bladder carcinoma. They were compared with a group of normal individuals. Ten patients were studied in each group.

Control group

These were all normal individuals with no previous

Based on a Poster Demonstration at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991 history of erectile dysfunction, urinary incontinence or diabetes. Their mean age was 61.2 years (range 51–72).

Nerve-sparing radical prostatectomy group

All 10 patients had undergone bilateral nerve-sparing radical prostatectomy for localised prostatic carcinoma (1 T1, 8 T2, 1 T3). Their mean age was 70.2 years (range 60–79). The mean time interval between surgery and neurophysiological studies was 11.8 months. None of the patients had nodal or bony metastasis. One patient had previously undergone a course of radical external beam radiotherapy to the prostate and 4 had erectile dysfunction pre-operatively. In no case was there evidence of disease recurrence or progression and the serum prostatic specific antigen was <4.4 μg/l (using Hybritech Tandem R radioimmunometric assay) at the time of the sphincter EMG tests.

Radical cystoprostatectomy group

All 10 patients had invasive transitional cell bladder carcinoma (T2–T3). Their mean age was 69.7 years (range 58–76) and the mean time interval between surgery and neurophysiological studies was 29.4 months. Five patients had undergone a course of external beam radiotherapy which had failed to eradicate the disease. All patients had undergone non-nerve-sparing radical total cystoprostatectomy and ileal conduit urinary diversion. Two patients had perineal urethrectomies for urethral tumour recurrences subsequently; 5 had had erectile dysfunction pre-operatively. No patient had clinical evidence of disease progression at the time of the sphincter EMG tests.

Four of 6 patients who were potent pre-operatively in the radical prostatectomy group remained potent (*i.e.* sufficiently rigid erections for intercourse) at the time of the neurophysiological tests but all 5 patients who were potent pre-operatively in the cystoprostatectomy group became impotent. One patient in the radical prostatectomy group was stress incontinent at 9 months and was successfully treated by insertion of an artificial urinary sphincter. Assessment of continence was not possible in the cystoprostatectomy group because of their urinary diversion.

The sphincter neurophysiological studies were performed using Medelec Mystro MS 20 in all cases. Three neurophysiological tests were carried out with the patient lying in the supine position: (1) motor unit analysis, (2) sacral reflex latency (equivalent to bulbocavernosus reflex), (3) pudendal somatosensory evoked potential.

Motor unit analysis (MUA)

A concentric needle electrode was inserted transperineally in the midline in an antero-cranial direction towards the apex of the prostate (sometimes guided by a rectal finger) until the typical burst of activity followed by repetitive tonically firing units of the urethral sphincter were recorded. After ensuring the correct position of the needle by listening for the characteristic tonic activity of the striated sphincter on the audio output of the electrophysiological recording unit, 10 consecutive different motor units (Fig. 1) were recorded by slightly adjusting the needle in different directions within the sphincter as suggested by Fowler *et al.* (1984). These units were then automatically analysed by the built-in computer and calculations made for each unit in terms of duration (ms), amplitude (mV) and area (mV.ms). The mean values of these measurements were calculated for each patient (Fig. 2).

Sacral reflex latency (SRL)

The reflex was elicited by stimulating the dorsal

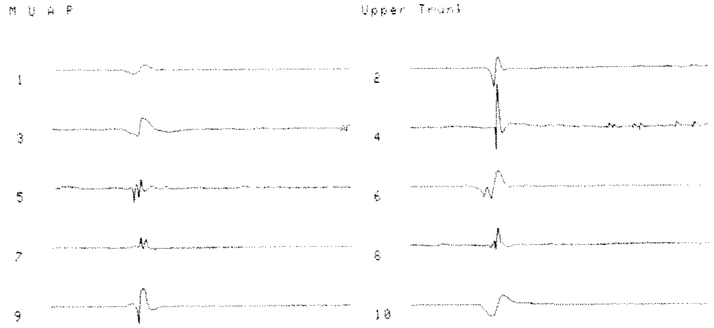
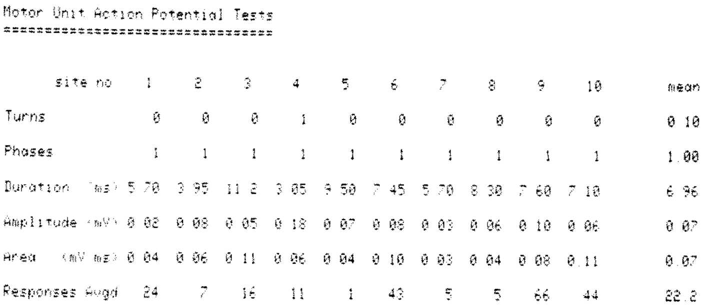


Fig. 1 Typical recording of motor unit analysis (10 units).



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Motor Unit Action Potential Tests
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      site no    1     2     3     4     5     6     7     8     9     10        mean

Turns            0     0     0     1     0     0     0     0     0     0         0.10

Phases           1     1     1     1     1     1     1     1     1     1         1.00

Duration  (ms) 5.70  3.95  11.2  3.05  9.50  7.45  5.70  8.30  7.60  7.10        6.96

Amplitude (mV) 0.02  0.08  0.05  0.18  0.07  0.09  0.03  0.06  0.10  0.06        0.07

Area   (mV ms) 0.04  0.06  0.11  0.06  0.04  0.10  0.03  0.04  0.08  0.11        0.07

Responses Avgd  24     7    16    11     1    43     5     5    66    44         22.2
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Fig. 2 Computerised analysis of motor units in Figure 5 measuring duration, amplitude and area of the units and their mean values.

nerve of the penis (Vodusek and Light, 1983) and recording with the same concentric needle electrode inserted for the above motor unit analysis. Square wave stimuli of 0.1 ms in duration were applied at a frequency of 1 Hz and the stimulus intensity was gradually increased from zero up to the threshold of sensation, which was recorded. The stimulus was then further increased until a response was recorded in the urethral sphincter or until the stimulus became too strong for the patient to tolerate; the intensity of the stimulus required is usually 2 to 3 times the sensory threshold. A minimum of 10 responses were recorded and the shortest onset latency was then calculated. A latency response < 35 ms was taken as normal (Fig. 3).

Examination of this reflex will allow analysis of the sacral segmental neural pathways S2 to S4.

Pudendal somatosensory evoked potential (SSEP)

A cortical response can be readily recorded following stimulation of the pudendal nerve (Opsomer *et al.*, 1986). This will allow analysis of the suprasacral neural pathways in patients with possible central lesions (Fig. 4).

The dorsal nerve of the penis was stimulated in the same way as used in SRL and the response was recorded using silver/silver chloride disc electrodes over the scalp. A variable intensity (2–4 × sensory threshold) was used at a rate of 2 Hz (Opsomer *et al.*, 1986; Vodusek, 1990) and recordings made at Cz (vertex) and referred to Fz (midline over forehead). The response to a minimum of 128 stimuli was amplified and displayed on the recorder. If a clear response was not seen at this time, stimulation was continued until a maximum of 256 stimuli had been applied. The procedure was then repeated once more to ensure reproducibility and the average latency was recorded. To minimise background myogenic activity during recording, the patients were asked to relax as much as possible, and in particular to close their eyes and relax their jaw muscles.

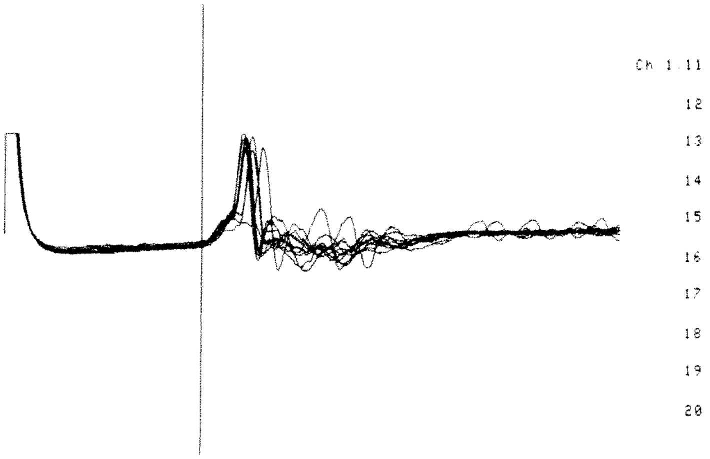

Fig. 3 Example of sacral reflex latency recordings showing consistent first response latencies (superimposed).

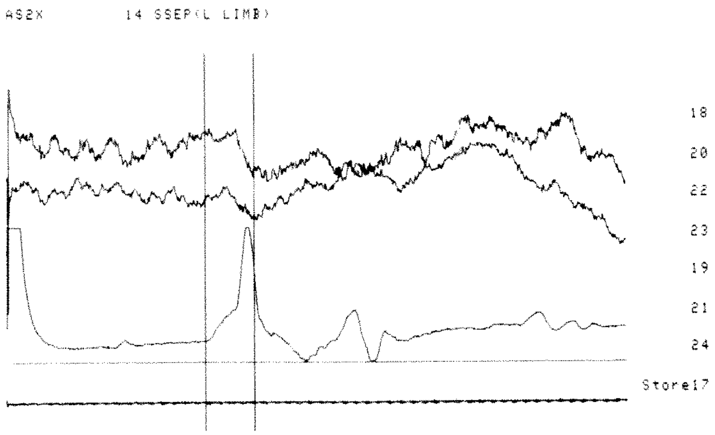

Fig. 4 Example of pudendal somatosensory evoked potential recordings.

Statistical analysis was carried out using non-parametric Mann Whitney U tests with 95% confidence intervals and the level of significance was taken as 5%.

Results

The results (duration and amplitude of MUA, SRL and pudendal SSEP) are illustrated in the scattergrams (Figs 5, 6, 7 and 8). The means and ranges of these parameters are summarised in Table 1. Results of the statistical analysis by Mann Whitney U tests are illustrated in Table 2.

The results of motor unit analysis showed a statistically significant difference in duration between the control and prostatectomy group (95% confidence intervals = −4.22, −1.99, $P = 0.0004$) and between the control and cystoprostatectomy group (95% confidence intervals = −4.62, −2.32, $P = 0.0003$). However, there was no significant difference in duration of the motor units (95% confidence intervals = −1.30, 1.10, $P = 0.73$) between the 2 operated groups. Analysis of the amplitude of the motor units showed no significant difference between all 3 groups. There was no significant difference in both sacral reflex latency and pudendal somatosensory evoked potential between all 3 groups, although we were able to elicit SSEP responses in only 8 patients in the prostatectomy group and 7 in the cystoprostatectomy group.

One patient in the radical prostatectomy group has a markedly prolonged SRL (73 ms) and an absent somatosensory evoked response.

Two patients in the cystoprostatectomy group who also had radical perineal urethrectomies showed abnormal SRL (49 and 54 ms) and no demonstratable SSEP.

Discussion

It is well established that the urethral sphincter muscle fibres are much smaller than those of the adjacent levator ani muscle (Gosling *et al.*, 1981) and this probably accounts for their characteristic EMG features. Although the range of published "normal" values is wide, the difference in duration of the motor units between the control group and the operated groups was highly significant. There was no significant difference in amplitude of the units between the 3 groups, but this may be explained by the fact that accurate measurement of amplitude requires more precise placement of the needle electrode than is required for the measurement of duration. In fact, statistical comparison between the control and the cystoprostatectomy patients in terms of motor unit amplitude showed 95% confidence intervals of −0.12 and 0 with a P value of 0.054, which approaches statistical significance. Furthermore, it is arguable whether the potential damage to the musculature of the urethral sphincter by surgery may account for the change in duration of the MUA. However, since primary muscle disorders normally produce shortened duration rather than prolongation of the motor units, our findings are almost certainly suggestive of a neurogenic aetiology.

If one accepts the mean of normal human sacral reflex latency as 35 ms, with a range of 24.4 to 44.8 ms (Bilkey *et al.*, 1983; Vodusek and Light, 1983), both of our operated groups would be normal in their mean SRL (37.3 ms for the prostatectomy

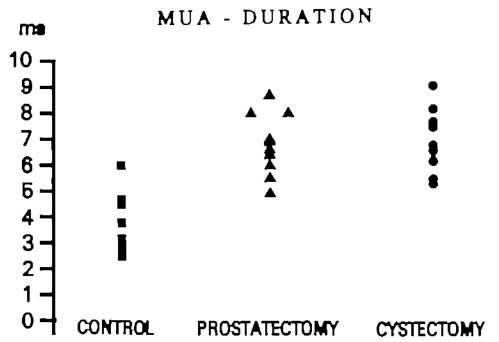

Fig. 5 Distribution of the mean duration of the motor units.

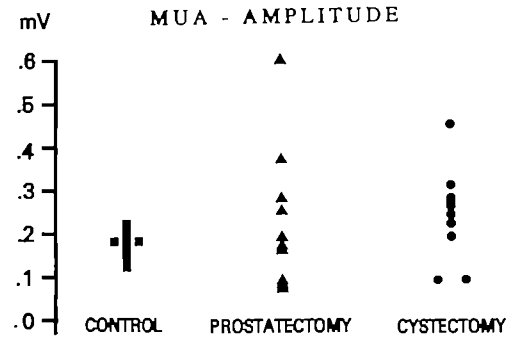

Fig. 6 Distribution of the mean amplitude of the motor units.

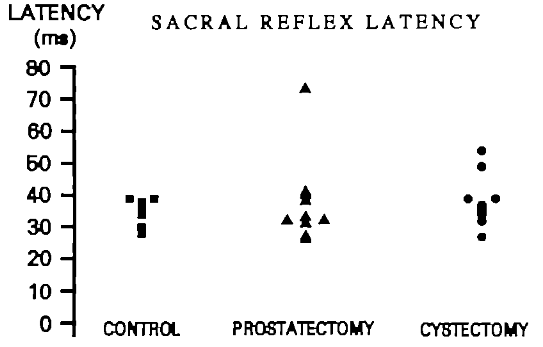

Fig. 7 Distribution of the mean SRL.

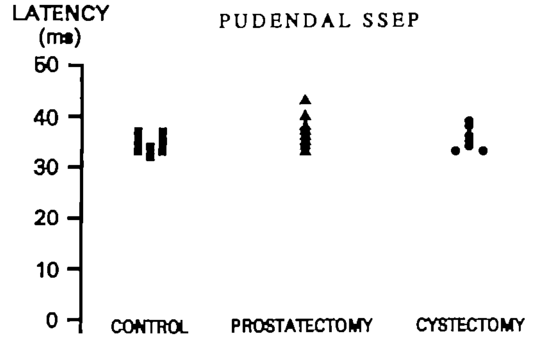

Fig. 8 Distribution of the mean SSEP latency.

and 38.2 ms for the cystoprostatectomy group) when compared with the control group (34.5 ms). Consequently, statistical analysis between the 3 groups showed no significant difference. However, what should be the upper limit of normal SRL is still debatable and varies between different neurophysiology departments.

Furthermore, the SRL is rather a crude assessment of the sacral segmental pathways and certainly partial or incomplete denervation of the pudendal nerve can coexist with a normal SRL (Blaivas *et al.*, 1981; Bilkey *et al.*, 1983), since SRL reflects only activity of the fastest conducting fibres in the reflex arc. It is interesting to note that 1 and 2 patients in the prostatectomy and the cystoprostatectomy group respectively had an SRL above 44.8 ms. The patient in the former group had stress incontinence post-operatively and both patients in the latter group had radical perineal urethrectomies.

For the pudendal somatosensory evoked potentail, we were not able to demonstrate any response in 5/20 patients in the operated groups (2 in the prostatectomy group and 3 in the cystoprostatectomy group), although statistical analysis of the remaining patients showed no significant difference from the control group. Apart from abnormal neural conduction, an "absent" response may result from inability of the patient to relax during the test. It is interesting that the patient with stress incontinence in the prostatectomy group and the 2 patients who had radical urethrectomies in the cystoprostatectomy group had no elicitable response.

The only patient with urinary incontinence in the nerve-sparing radical prostatectomy group had prolonged SRL and absent SSEP, indicating abnormal pudendal nerve conduction. Since there was no clinical evidence of local recurrent or residual prostatic carcinoma, surgical trauma (especially around the sphincter and pelvic floor) would be the most likely cause of this abnormality. Similarly, the 2 patients with perineal urethrectomies in the cystoprostatectomy group had prolonged SRL and absent SSEP and their pudendal nerves (or their branches) were probably traumatised during surgery.

Six patients had pre-operative radiotherapy to the pelvis (1 in the prostatectomy and 5 in the cystoprostatectomy group) and radiation neuritis could be a potential cause of EMG abnormalities. However, only 1 patient (cystoprostatectomy group) showed absent SSEP but normal SRL, raising the possibility of suprasacral (central) neural deficit rather than segmental.

Table 1 Summarised Results of Means and Ranges of MUA, SRL and SSEP

	Motor unit analysis							
	Duration (ms)		*Amplitude (mV)*		*SRL (ms)*		*Pudendal SSEP (ms)*	
Group	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*
Control	3.7	2.4–6.0	0.18	0.12–0.22	34.5	28–39	34.6	32.4–37.3
Prostatectomy	6.8	5.5–8.7	0.23	0.07–0.60	37.3	26–73	36.9	32.8–43.1
Cystoprostatectomy	7.1	5.3–9.1	0.24	0.09–0.45	38.2	27–54	36.8	33.4–42.8

Table 2 Summary of Statistical Analysis by Mann Whitney U tests with 95% confidence intervals and P values

	Motor unit analysis			
Group	*Duration*	*Amplitude*	*SRL*	*Pudendal SSEP*
Control *vs* prostatectomy	−4.22, −1.99 $P = 0.0004$	−0.12, 0.07 $P = 0.8798$	−5.00, 6.01 $P = 1.00$	−4.34, 0.40 $P = 0.1405$
Control *vs* cystectomy	−4.62, −2.32 $P = 0.0003$	−0.12, 0.00 $P = 0.0539$	−10.00, 2.00 $P = 0.43$	−4.20, 0.40 $P = 0.1041$
Prostatectomy *vs* cystectomy	−1.30, 1.10 $P = 0.7337$	−0.15, 0.09 $P = 0.4274$	−9.00, 5.00 $P = 0.41$	−2.50, 2.80 $P = 0.7624$

The post-operative potency rate (4/6) in the radical prostatectomy group conformed reasonably well to the rates reported by other centres performing this operation. Not surprisingly, none of the patients in the cystoprostatectomy group was potent post-operatively, since the operations were non-nerve-sparing. It is interesting to note that 5 of the other 6 patients who had erectile dysfunction (4 of whom were affected pre-operatively) were continent post-operatively–tentative evidence to support the fact that the cavernous nerve does not innervate the distal urethral sphincter. Although we were unable to assess continence in the cystoprostatectomy group, the fact that there was no significant difference in all MUA, SRL and SSEP parameters between the 2 operated groups strongly supports the foregoing hypothesis.

These results suggest that the nerve fibres routed through the neurovascular bundles of Walsh are mainly concerned with innervation of the corporal bodies. Their division when clinically indicated, therefore, is liable to induce erectile dysfunction but should not compromise distal urethral sphincter function. Together with Kirby *et al.* (1986), we recommend the use of urethral sphincter EMG to provide an effective means of assessing damage to vesicourethral innervation as a result of previous surgery.

It was concluded that motor unit analysis of the external urethral sphincter showed a significantly prolonged duration in patients after radical prostatectomy or radical cystoprostatectomy when compared with control patients. There was no significant difference in sphincter EMG findings between nerve-sparing radical prostatectomy and non-nerve-sparing radical cystoprostatectomy patients. Division of the cavernous nerve of Walsh did not compromise distal urethral sphincter function. Radical transabdominal lower urinary tract surgery may induce significant EMG changes in the external urethral sphincter which may not be clinically evident. This may affect continence later if second-stage urinary reconstructive surgery is undertaken.

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Comparison of Effects following the Intracorporeal Injection of Papaverine and Prostaglandin E_1

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Summary—A study group of 240 impotent men receiving intracorporeal injections were divided into 2 groups: the first group received papaverine (60 mg) and the second prostaglandin E_1 (PGE_1 20 μg). The effect of the drugs was evaluated according to the onset of erection, rigidity and the duration of erection; 136 patients were treated with papaverine and 104 with PGE_1. The onset of action in these groups was 6.42 ± 5.39 *vs* 10.14 ± 5.41 min; the rigidity score was 3.37 ± 0.89 *vs* 3.60 ± 1.10 and the duration of erection was 49.56 ± 62.56 *vs* 63.60 ± 44.57 min respectively. There was a significant difference in the onset of action (PGE_1 was slower than papaverine) and maintenance of erection (longer with PGE_1 than with papaverine). Another group of 17 patients received both papaverine and PGE_1. The effects of papaverine were better in 4 cases, worse in 5 and equal to PGE_1 in 8. This study indicates that compared with papaverine, treatment with PGE_1 produces a slower onset of action, a longer duration of erection and fewer side effects.

Dilatation of arterial trees, expansion of the sinusoids and compression of the subtunical and emissary veins constitute the major mechanisms of erection (Lue and Tanagho, 1987), with smooth muscle in the arteriolar trees and the trabeculae playing a key role in the erectile process (Lue, 1986). The discovery that vasoactive agents injected into the corpus cavernosum can induce penile erection has marked a new era in the management of impotence. The administration of papaverine, alone or in combination with other vasoactive agents and as part of the differential diagnosis and/or management, has been discussed previously (Nellans *et al.*, 1987; Keogh *et al.*, 1989). Initially, these agents were reported to induce systemic reactions such as dizziness, facial flushing, hypotension and priapism (Sidi, 1988). More recently, however, reduced dosages have led to a considerable reduction in side effects (Earle *et al.*, 1990; Lakin *et al.*, 1990). Prostaglandin E_1 (PGE_1) is a physiological agent that is metabolised locally within the cavernous tissue (Roy *et al.*, 1984). Neither systemic reactions nor priapism were noted in previous studies (Stackl *et al.*, 1988; Hwang *et al.*, 1989a and b). However, large doses of PGE_1 were reported to induce prolonged erection or priapism in impotent patients, especially in psychogenic or neurogenic cases (Schramek *et al.*, 1990). In this study we have compared the effects of the intracorporeal injection of papaverine and PGE_1.

Patients and Methods

A total of 240 impotent men received intracorporeal injections between September 1987 and June 1989; 136 patients (aged 25–79 years; mean 57.3) were treated with papaverine and 104 patients (aged 22–82 years; mean 54.5) were treated with PGE_1. A general history was taken and physical examination and hormonal surveys (T3, T4, testosterone, prolactin and follicle-stimulating and luteinising hormones) were carried out routinely. Nocturnal penile tumescence was measured with a nocturnal penile tumescence device (Browne Corporation, Santa Barbara, USA) or Snap-Gauge band (Dacomed, Minneapolis, USA). The various aetiologies were

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distributed almost equally between the 2 groups. Patients were assigned randomly either to the papaverine group or to the PGE_1 group and were studied consecutively thereafter. The whole procedure and its possible side effects were explained in detail to each patient and written consent was obtained.

Papaverine 60 mg (or PGE_1 20 μg) was dissolved in 2 ml distilled water before being injected into the corpus cavernosum. The patient was placed in a comfortable supine position with a rubber band placed at the base of the penis. The site of injection, which was about 2 cm from the glans penis, was cleansed with an alcohol swab. The vasoactive agent was injected intracorporeally with a 27 gauge needle at 45° through the lateral aspect of the penis. The puncture site was then compressed until the band was removed 2 min later. The patient was required to stand for a minimum of 5 min and was instructed to return to the emergency department if erection persisted for more than 4 h.

The degree of response (positive, poor or no response), onset of action, penile rigidity (score 0–5) and maintenance of erection were recorded. A positive response was defined as a full erection following the injection of papaverine or PGE_1 and persisting for more than 30 min. Complications such as facial flushing, pain, dizziness, haematoma, prolonged erection and priapism were recorded. The effects of papaverine and PGE_1 were compared using the independent *t* test. Average values of onset of action, rigidity and maintenance of erection were presented as the mean and standard deviation.

A third group of 17 patients received injections of papaverine (60 mg) and PGE_1 (20 μg) alternately. The underlying aetiologies in these patients were as follows: vasculogenic (13), diabetic (2), trauma (1) and psychogenic (1). The effects of papaverine and PGE_1 were also compared individually, considering both objective and subjective evidence (*i.e.* patients' verbal reports). An agent was considered to be superior if it induced better rigidity and a longer duration of erection (objective evidence) and if the patient himself reported that he felt better (subjective evidence). In the absence of a significant difference between the 2 agents, their efficacy was considered to be equal.

Results

Table 1 shows that there was no significant difference between the papaverine group and the PGE_1 group with regard to age, risk factor and the distribution of underlying aetiology. In the papaverine group a positive response was found in 74 patients (54.4%) and in the PGE_1 group a positive response was found in 73 patients (70.2%) (Table 2).

Significant differences between these 2 groups were found in the onset of action ($P<0.001$) and in the maintenance of erection ($P<0.05$) (Table 2). The response rate among diabetics was only 37.5% in the papaverine group and 60% in the PGE_1 group.

In the papaverine group the following complications were found: haematoma (n = 4; 2.9%), priapism (n = 4; 2.9%), pain (n = 11; 8.1%), facial flushing (n = 4; 2.9%) and dizziness (n = 3; 2.2%). All patients with priapism were in the vasculogenic group. Spontaneous detumescence was achieved after aspiration of the corpus cavernosum and there were no subsequent complications. Venous leakage was documented in only one of the 4 patients with facial flushing and another one in the 3 patients with dizziness. In the PGE_1 group, haematoma was found in 4 patients (3.8%) and pain in 19 (18.3%); there was no facial flushing, dizziness or priapism; 0.5 ml 1% lignocaine was added to the PGE_1 solution for patients who reported pain after the intracorporeal injection and this produced partial pain relief.

Among the 17 patients who were treated with both agents, the effects of papaverine were better in 4 cases, worse in 5 and equal to PGE_1 in 8. Thirteen of the 17 patients who were in the vasculogenic group claimed that papaverine produced better effects in 3 cases, worse effects in 5 and was equal to PGE_1 in 5.

Discussion

Papaverine hydrochloride is the salt of a benzylisoquinoline alkaloid that can be either synthesised or obtained from opium. It is a potent, non-specific smooth muscle relaxant that directly affects muscles regardless of their innervation. Its effects are greatest on smooth muscle in the vascular, bronchial, gastrointestinal, biliary and urinary systems. PGE_1, a powerful smooth muscle relaxant (Hedlund and Anderson, 1985), is a natural constituent of many mammalian tissues (Piper, 1973). Roy *et al.* (1984) reported that human cavernous tissue can generate prostaglandin and thromboxanes *in vitro*. In the treatment of severe peripheral vascular disease it has been used clinically with reasonable success in improving the microcirculation. Hedlund and Anderson (1985) found that PGE_1 was the most appropriate agent for relaxation of the

Table 1 Aetiology in Papaverine and PGE_1 Groups

Aetiology	*Papaverine group (n = 136)* *No. (%)*	*PGE_1 group (n = 104)* *No. (%)*
Vascular	70 (57.5)	56 (53.8)
Hypertension	17 (12.5)	13 (12.5)
Diabetes	8 (5.9)	10 (9.6)
Atherosclerosis	14 (10.3)	10 (9.6)
Hyperlipidaemia	2 (1.5)	2 (1.9)
Abnormal Xenon-133 washout study	28 (20.4)	21 (20.2)
Renal insufficiency	1 (0.7)	0 (0.0)
Psychogenic	24 (17.6)	19 (18.3)
Neurogenic	7 (5.1)	8 (7.7)
Post-operative	5 (3.7)	6 (5.8)
Spinal cord injury	2 (1.5)	2 (1.9)
Hormonal	5 (3.7)	5 (4.8)
Hyperprolactinaemia	2 (1.5)	3 (2.9)
Hypogonadism	3 (2.2)	2 (1.9)
Undetermined	26 (19.1)	15 (14.4)
Pre-APR* evaluation	4 (2.9)	1 (1.0)

* APR: abdominoperitoneal resection.

cavernous artery and the erectile tissue proper (corpus cavernosum and corpus spongiosum) *in vitro*. Whether arterially or intracavernously administered, PGE_1 is rapidly metabolised and distributed through the body except for the central nervous system (Stackl *et al.*, 1988). In a single passage through the lungs, approximately 70% of PGE_1 is metabolised (Gloub *et al.*, 1975). This rapid metabolism is responsible for the lack of systemic reactions.

Impotence in the positive response group was either psychogenic or neurogenic in origin, or was caused by mild arterial occlusion that did not seriously hamper blood delivery to the cavernous bodies. The response rate in our psychogenic and neurogenic groups was almost the same as the 100% reported by Sidi (1988). Although the same dosage (papaverine 60 mg or PGE_1 20 µg) was given to all of the psychogenic or neurogenic patients for investigative comparison in the present study, it is preferable to use a reduced dose for these groups. Our data indicated that only 37.5% of the diabetic patients responded to papaverine and 60% responded to PGE_1. These findings are similar to those of Ishii *et al.* (1989).

Although no significant difference in rigidity was shown between these 2 groups, the positive rate was higher in the PGE_1 group (72.0% *vs* 54.4%) and maintenance of erection was longer (Table 2). These results might mean that the vascular response to PGE_1 is stronger. Furthermore, the slower onset observed in the PGE_1 group might be due to different intracorporeal mechanisms between these 2 agents. In our previous penile blood flow study, conducted by duplex sonography, PGE_1 was associated with a stronger vascular effect (as indicated by peak blood velocity and increased diameter of cavernous arteries), which demonstrates another

Table 2 Vasoactive Effects of Papaverine and PGE_1

	Onset of action (min)		*Rigidity score**		*Maintenance of erection (min)*	
	Average	*Range*	*Average*	*Range*	*Average*	*Range*
Papaverine (60 mg)	6.42 ± 5.39	1–60	3.37 ± 0.88	0–5	49.56 ± 62.56	2–360
PGE_1 (20 µg)	10.41 ± 5.41†	1–32	3.60 ± 1.10	0–5	63.60 ± 44.57‡	9–240

* Score: 0 = no response. 1 = elongation. 2 = tumescence. 3 = partial rigidity sufficient for vaginal penetration. 4 = partial rigidity, erection angle < 90°. 5 = full rigidity.
‡ $P<0.05$. † $P<0.001$.

advantage of PGE$_1$ (Hwang *et al.*, 1989a and b). Comparison between papaverine and PGE$_1$ indicated that the incidence of adverse side effects was less frequent in the PGE$_1$ group.

Another group of 17 patients who received both drugs showed no significant difference either objectively or subjectively, but the small sample size makes these results very tentative.

In our limited experience with papaverine, we have found that its therapeutic range is small, resulting in an increased risk of priapism. However, compared with other vasoactive intracorporeal drugs, the safety range of PGE$_1$ was wide and the side effects were minimal. A double dose (40 µg) was given to all patients who responded poorly to single doses and no additional complaints of discomfort were noted, even from the 2 patients who had primary impotence with obvious venous leakage.

None of the patients receiving PGE$_1$ required treatment for prolonged erection. The absence of these undesirable side effects is thought to be the result of intravascular metabolism processed intracorporeally (Stackl *et al.*, 1988). However, care must be taken in diagnosis and treatment, especially in disorders of psychogenic and neurogenic origin. The dosage used in the present study could cause prolonged erection or even priapism in some patients (Schramek et al., 1990; Watters *et al.*, 1990).

A tolerable degree of pain occurred during injection or erection in the PGE$_1$ group (18.3%) and this was reduced by adding 0.5 ml 1% lignocaine to the PGE$_1$ solution.

In conclusion, although papaverine and PGE$_1$ had an almost equal effect on rigidity, PGE$_1$ produced fewer side effects, was slower in onset and sometimes produced a longer duration of erection. We believe that PGE$_1$ could be an acceptable alternative in vasoactive intracorporeal pharmacotherapy, although the cost is considerably higher (32 *vs* 5 US dollars for 1 injection). Longer clinical follow-up and further studies (*e.g.* on histopathological changes) are required before firm conclusions can be drawn.

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Combined Papaverine Test and Radionuclide Penile Blood Flow in Impotence: Method and Preliminary Results

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Summary—The investigation of vascular impotence requires a simple, reliable and non-invasive method of estimating penile arterial supply. A method for measuring flow to the dependent portion of the penis has been developed using technetium-labelled red blood cells (^{99m}Tc-RBC). Its use, in conjunction with the intracavernous injection of papaverine, was investigated in 32 patients with various causes of impotence.

Intracavernous papaverine was administered and a pneumatic cuff was inflated around the base of the penis both to isolate the penile circulation and to prevent dispersion of papaverine. The remaining blood pool was labelled with ^{99m}Tc-RBC. A gamma camera was used to produce a time–activity curve for the penis following release of the cuff. Penile blood flow was calculated from the initial gradient of the time–activity curve.

Papaverine-stimulated penile blood flow was significantly greater in patients without evidence of arterial insufficiency. None of the subjects with arterial disease achieved flows greater than 20 ml/min/100 ml, while flow in patients without arterial disease exceeded this value. Flow estimation without the use of papaverine was not able reliably to discriminate between the 2 groups.

There was no difference in papaverine-stimulated blood flow between impotent subjects with veno-sinusoidal leakage, in the absence of arterial disease, and a control group who achieved full erection with papaverine. It was therefore possible, by assessing the response to papaverine and measuring arterial blood flow, to distinguish between arterial insufficiency, veno-sinusoidal leakage and non-vascular causes of impotence.

The method requires little skill and can be modified for use with inexpensive equipment.

Normal penile erection requires the co-ordinated function of neurological, arterial and venous systems and, even if these systems are intact, the process may be inhibited by psychological factors.

The intracavernous injection of vasodilators such as papaverine or phentolamine results in erection in normal subjects. This is the basis of the papaverine test which has proved valuable in the investigation of impotence. The response to papaverine should be normal in neurological or psychological disease (Virag *et al.*, 1984). Exceptions have been reported in severe anxiety states (Buvat *et al.*, 1986), but the test remains a useful out-patient screening procedure. Failure to respond to adequate doses of intracavernous vasodilators suggests either arterial insufficiency or veno-sinusoidal leakage. The differentiation of these 2 conditions has previously required either invasive investigation such as arteriography and cavernosography or the use of the penile/brachial systolic pressure index (PBI), the accuracy of which has been questioned (Aitchison *et al.*, 1990). Arteriography can provide excellent detail of penile arterial anatomy but provides no functional information and is technically demanding. Disease in small vessels may not be demonstrated arteriographically.

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The assessment of penile arterial supply by duplex scanning of the penile arteries has recently received attention (Lue *et al.*, 1985; Collins and Lewandowski, 1987; Robinson *et al.*, 1989). The technique is potentially of value in the diagnosis of vasculogenic impotence but problems are encountered due to variations in arterial anatomy, which are common in the penis, and in the timing of the measurement in relation to injected vasodilators. Duplex studies generally are subject to operator dependence, and assessment of the penile vasculature is technically demanding.

Radionuclide techniques in the evaluation of penile blood flow can potentially supply functional information that is not influenced by normal variations in anatomy. The effects of small vessel disease would be detectable and the studies could be used to assess the results of arterial surgery. In common with other radionuclide techniques, such studies would not require a high level of operator skill and the measurements should be reproducible. Several attempts have been made to assess penile arterial supply by radionuclide techniques but, as discussed below, the methods used leave many of these studies open to criticism.

We have assessed the arterial supply to the dependent portion of the penis by the combined use of intracavernous papaverine and blood pool imaging. Penile blood flow both in the flaccid state and in the early erection phase of maximum blood flow was measured. The ability of this test to distinguish between penile arterial insufficiency and other causes of impotence was investigated.

Patients and Methods

A prospective study was undertaken on out-patients referred to the urology clinic for the investigation of impotence. A full history and clinical examination were performed and blood glucose, testosterone and prolactin were measured. Evidence of hypertension, diabetes, coronary artery disease, peripheral vascular disease and previous vascular surgery involving the iliac arteries was sought since these were considered possible indicators of penile vascular insufficiency.

Patients were categorised into 1 of 4 diagnostic groups on the basis of clinical findings, response to intracavernous papaverine and, where appropriate, cavernosography and arteriography.

Cavernosography was carried out on all patients in whom the papaverine response was subnormal unless a prior diagnosis of arterial insufficiency had already been made. A modification of the method of Lue *et al.* (1986) was used: 60 mg of papaverine were injected into the left corpus cavernosum via a 19G needle with a clamp applied to the base of the penis to prevent dispersion. After a 10-min interval the clamp was removed and dilute contrast agent infused, commencing at a rate of 15 ml/min and the rate doubled in a stepwise fashion until erection was achieved. The rate to maintain erection was recorded and radiographs taken in the PA and oblique projections. A maintenance rate of less than 30 ml/min with no sustained opacification of the draining veins was considered normal.

Aortography with selective bilateral internal iliac catheterisation was undertaken using intra-arterial papaverine to improve penile vessel visualisation. Indications for arteriography included a strong clinical suspicion of arterial disease, failure to respond to 60 mg papaverine in the presence of a normal cavernosogram and where indicated independently for the investigation of lower limb occlusive vascular disease, but it was only undertaken when appropriate with regard to the patient's age and general health.

Penile blood flow was measured by a modification of the limb blood flow method of Parkin *et al.* (1986). Intravenous stannous medronate (Amerscan Stannous Agent) was administered in the recommended dose of 0.03 ml/kg 30 min prior to the study to enable *in vivo* red cell labelling. The subjects were positioned under a gamma camera with a lead rubber sheet placed beneath the penis to shield the camera from radiation emitted from the scrotum and thighs. A 19 mm wide inflatable cuff (D. E. Hokanson, Issaquah, Washington, USA) was applied to the base of the penis and inflated to 250 mmHg pressure. Loosely applied adhesive tape was used to keep the penis immobile. Papaverine hydrochloride (60 mg intracavernous injection) was administered and allowed to act for 10 min with the cuff remaining inflated. At 7 min a 925 MBq bolus of ^{99m}Tc was injected intravenously and images of the lower pelvis and penis were recorded every second; this was to ensure effective isolation of the penile circulation. At 10 min a venous sample was collected to assess blood pool activity and the penile cuff was deflated. Images were recorded for a further 3 min. A region of interest was selected to include the dependent portion of the penis distal to the proximal edge of the cuff. Count rates in this region were plotted against time and a "best fit" line was drawn through the values of the initial straight line portion of the curve (Fig. 1). This initial portion of the curve represented the rate of activity increase immediately following deflation

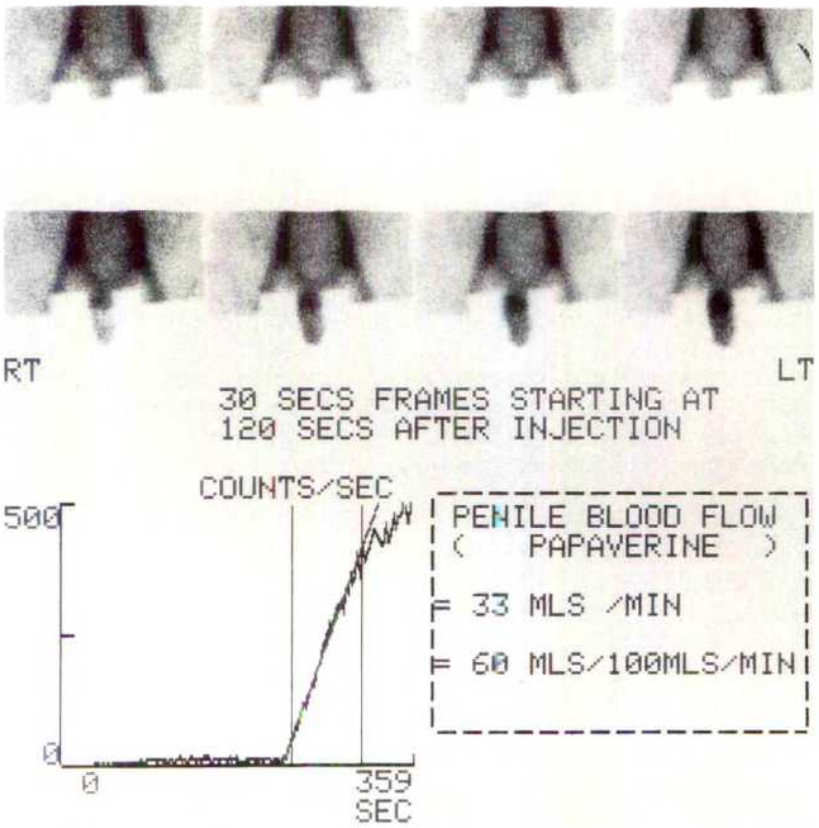

Fig. 1 Papaverine stimulated penile blood flow study in Case 2 (control). Each frame represents the composite images of thirty 1-s acquisitions. The upper row of frames was produced before cuff deflation and shows no activity in the penis distal to the proximal edge of the cuff. The lower row was obtained after cuff deflation. The time–activity curve shows the gradient immediately following cuff deflation from which the flow has been calculated.

of the cuff and was used to calculate the blood inflow. Blood pool activity was measured by placing the withdrawn sample, in a 10 ml syringe, directly on the collimator of the gamma camera.

If the gradient of the initial portion of the curve is G counts/s/s, blood pool activity is C counts/s/ml and penile volume is V ml then the flow, F, is $(G/C \times 100/V)$ ml/s/100 ml. No correction factor for self-absorption is applied because the self-attenuation of activity in the penis is similar to that in the 10-ml syringe and both values are negligible. For the purpose of the study penile shape was assumed to be cylindrical and volume was assessed by measuring the length and circumference of the dependent portion in the flaccid state.

Papaverine-induced erection was assessed by observation in the standing position and palpation 20 min after cuff deflation. A full and sustained erection, judged sufficient for intercourse by both observer and patient, was considered a normal response.

The subjects were re-examined at an interval of at least 1 week with an identical period of cuff inflation but without papaverine injection. The second study provided an unstimulated penile blood flow measurement.

The validity of the method was tested by constructing a phantom consisting of a partially water-filled balloon into which water labelled with ^{99m}Tc was instilled using a syringe pump.

Results

In all, 32 consecutive patients were studied. Penile blood flow was assessed with and without papaverine in 28 subjects and only following papaverine in a further 4 subjects (Tables 1 and 2; Fig. 2).

Control Group. Nine patients were considered to have a non-vasculogenic cause for impotence and acted as controls. Penile volume measurements were not available on 2 of these patients. Seven

Table 1 Details of Patients

Case	*Age (years)*	*Papaverine test**	*Unstimulated flow (ml/min/100 ml tissue)*	*Stimulated flow (ml/min/100 ml tissue)*	*Cavernosography (ml/min)†*
Controls					
1	36	3	12.3	25.4	—
2	32	3	16.7	60.0	—
3	69	3	—	—	—
4	22	3	—	—	—
5	55	3	20.0	54.7	—
6	43	3	11.1	23.4	5
7	40	3	8.4	21.2	30
8	60	1	—	26.0	15
9	28	2	10.1	24.4	0
Arterial					
10	53	1	4.2	10.8	—
11	51	2	7.2	16.7	—
12	52	1	5.9	15.9	>300
13	49	1	3.7	19.0	30
14	47	2	2.5	8.3	120
15	51	0	2.5	8.4	300
Venous					
16	61	1	24.0	38.5	>300
17	51	2	8.4	33.3	240
18	52	1	13.4	23.2	240
19	41	1	5.5	29.9	240
20	61	1	7.7	74.4	>300
21	58	2	9.4	58.1	120
22	56	1	5.3	35.5	>300
23	64	1	6.2	32.2	60
24	59	2	11.5	81.3	55
25	30	1	5.5	51.0	240
26	30	2	27.4	57.0	25
27	58	1	—	43.6	180
28	33	0	—	40.0	120
29	47	1	—	57.0	90
Unclassified					
30	37	1	5.2	21.7	180
31	40	1	2.4	17.9	40
32	24	2	5.5	17.9	6

*0 = no response
1 = Tumescent but not rigid
2 = Suboptimal rigidity
3 = Full sustained erection

†Flow required to maintain erection

patients achieved sustained firm erections with 60 mg papaverine (patients 1–7). Patient 8 did not respond fully to papaverine but gave a history of sustained morning erections and had a normal cavernosogram. Patient 9 also had a submaximal papaverine response but achieved full self-sustained erection during cavernosography. Penile blood flow without papaverine was 8.4–20.0 (mean 13, SD 4.4) ml/min/100 ml, increasing to 21.2–59.5 (mean 33.5, SD 16.2) ml/min/100 ml with papaverine.

The remaining 23 patients failed to achieve full erection with papaverine. These were classified into 3 groups according to the probable cause of their impotence.

Arterial insufficiency group. Six patients (10–15) were considered to have penile arterial insufficiency, though not necessarily as the sole cause of impotence. Patients 11 and 12 had undergone aorto-bifemoral bypass grafting for occlusive disease in the iliac arteries. Patient 14 had aorto-iliac disease on arteriography. Patient 15 had undergone renal transplantation on to an internal iliac artery and had clinical evidence of widespread vascular dis-

Table 2 Penile Blood Flow (mean ± SD), with and without Papaverine in the 4 Study Groups

	Penile blood flow (ml/min) mean ± SD			
	Without papaverine		*With papaverine*	
Clinical classification	*Total*	*Per 100 ml tissue*	*Total*	*Per 100 ml tissue*
Control	5.3 ± 2.9 (n = 8)	13.1 ± 4.4 (n = 6)	15.6 ± 7.6 (n = 9)	33.5 ± 16.2 (n = 7)
Arterial	1.8 ± 0.7 (n = 6)	4.3 ± 1.9 (n = 6)	5.7 ± 1.9 (n = 6)	13.2 ± 4.6 (n = 6)
Venous	5.9 ± 5.8 (n = 11)	11.3 ± 7.6 (n = 11)	21.0 ± 8.8 (n = 14)	46.8 ± 17.1 (n = 14)
Unknown	2.3 ± 0.9 (n = 3)	4.4 ± 1.7 (n = 3)	10.3 ± 0.2 (n = 3)	19.2 ± 2.2 (n = 3)

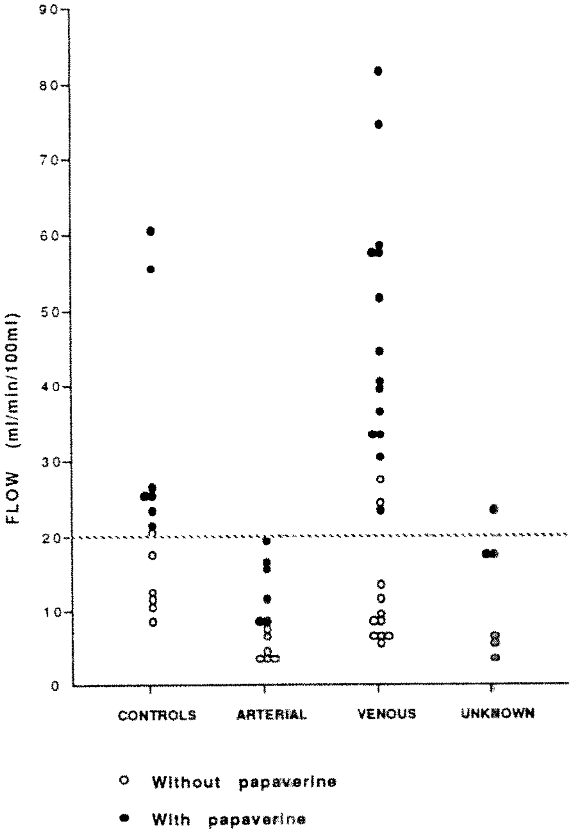

Fig. 2 Penile blood flow with and without papaverine in 4 study groups. A post-papaverine flow >20 ml/min/100 ml (interrupted line) was seen in patients without arterial disease.

ease. The remaining 2 patients (10 and 13) both had clinical evidence of severe widespread arterial disease. Cavernosography demonstrated veno-sinusoidal leakage in patients 12–15. Penile blood flow without papaverine was 2.5–7.2 (mean 4.3, SD 1.9) ml/min/100 ml, increasing to 8.3–19.0 (mean 13.2, SD 4.6) ml/min/100 ml after papaverine. Patient 13 underwent a second blood flow study with papaverine after unhelpful penile vein ligation but only the initial study was included in the statistical analysis. Stimulated penile blood flow was 8.4 ml/min/100 ml before and 10.9 ml/min/100 ml after surgery.

Venous leak group. Thirteen patients (16–29) were considered to have veno-sinusoidal leakage as the sole cause of impotence. None had any clinical features to suggest the presence of arterial disease. Patients 19 and 26 had normal arteriograms. Patient 26 was thought to have a normal cavernosogram but achieved a good result with penile vein ligation, performed as a last resort. The classification of this patient may not be strictly accurate but an arterial aetiology was excluded and the rationale for inclusion with this group is discussed below. The remainder had abnormal cavernosograms with excessive opacification of draining veins and an infusion requirement of more than 30 ml/min to maintain erection. Penile blood flow without papaverine was 5.5–27.4 (mean 11.3, SD 7.6) ml/min/100 ml and increased to 23.2–81.3 (mean 46.8, SD 17.1) ml/min/100 ml with papaverine.

Unknown aetiology. Three patients (30–32) could not be firmly classified on available evidence. Patient 30 associated his impotence with the onset of Raynaud's disease and scleroderma. Veno-sinusoidal leakage was demonstrated by cavernosography but venous ligation was unhelpful and an additional arterial aetiology was suspected on clinical grounds. Consent to arteriography was refused. Patient 31 had no clinical evidence or risk factors for arterial disease. Although cavernosography did show venous leakage, the infusion rate to maintain erection was only slightly excessive at 40 ml/min and he did not benefit from venous ligation on 2 occasions. An additional arterial aetiology was suspected but arteriography was normal. Patient 32 was an exceptionally anxious young man with no clinical evidence of arterial disease. He had a normal cavernosogram and had derived no benefit from previous venous ligation performed elsewhere. In these 3 patients penile blood flow following papaverine ranged between 17.9 and 21.7 ml/min/100 ml.

There was no significant difference in penile blood flow between the control and venous leak group, either in the unstimulated state ($P=0.605$) or following papaverine ($P=0.105$). Blood flow in the arterial disease group was significantly less than in the controls both in the unstimulated studies ($P=0.001$) and following papaverine ($P=0.013$). Unstimulated flow in the arterial disease group was less than in the venous leak group ($P=0.048$) and the difference was highly significant following papaverine ($P<0.001$). If only unstimulated measurements are considered there was some overlap in flow values between the arterial disease and venous leak groups. In the papaverine-stimulated studies none of the subjects with arterial disease exceeded a flow rate of 20 ml/min/100 ml, while all of the subjects without arterial disease exceeded this figure.

Studies conducted with the phantom showed that the method used to measure flow was accurate at the range of flows experienced in our study groups. At flows of less than 1 ml/min/100 ml the error exceeded 10% but such low values were not seen in the study population.

The images produced by the gamma camera were useful in confirming that the study was technically adequate but spatial resolution was insufficient to detect arterial stenosis or occlusion and no attempt was made to use the images for this purpose.

Two control patients (3 and 6) developed prolonged erections following papaverine and required cavernosal aspiration.

Discussion

The measurement of penile blood flow by the method described in this study demonstrated reduced perfusion of the dependent portion of the penis in patients with penile arterial insufficiency. Patients with isolated veno-sinusoidal leakage, without evidence of arterial disease, had penile blood flows similar to those of the control subjects. Where arterial disease and veno-sinusoidal leakage co-existed, the method was able to detect the presence of arterial insufficiency. In the single example studied (patient 15) penile vein ligation had no significant effect on the measurement of blood inflow. The detection of arterial disease in the presence of veno-sinusoidal leakage is important because the 2 conditions often co-exist and are difficult to differentiate since both result in a negative papaverine test. The presence of occult arterial insufficiency may partially explain the poor results of venous surgery for impotence.

The diagnosis of veno-sinusoidal leakage is generally made on the results of cavernosography and cavernosometry. The interpretation of these studies is critically dependent on technique. Differences in the use and dosage of vasodilators, restriction of vasodilator washout by the application of a ligature around the base of the penis and the time allowed for the vasodilator to act influence the results. Unfortunately a lack of standardisation has resulted in differences in quoted normal and abnormal ranges. Wespes *et al.* (1986) found that flow rates to maintain erection of up to 10 ml/min were not associated with venous leakage, while flows above 25 ml/min were found in impotent patients with leakage. Dickinson and Prior (1989) considered maintenance flow rates above 50 ml/min to be diagnostic of venous leakage, while patients who were able to maintain erection at a flow rate of less than 50 ml/min but were not able to sustain erection after perfusion were considered to have arterial insufficiency. We diagnosed venous leakage if the flow rate required to maintain erection was greater than 30 ml/min. This is broadly in agreement with other authors who use a similar technique. We also consider it relevant that flow rates above this value were associated with persistent opacification of pelvic veins while a flow requirement below this value was only associated with a transient or slight opacification.

For the purposes of this study patients with combined arterial insufficiency and veno-sinusoidal leakage were classified in the arterial disease category, since the objective was to determine the presence or absence of arterial disease whatever other abnormalities were present. As far as possible patients with arterial disease were deliberately excluded from the venous category although, in unselected patients with venous leakage a proportion would be expected also to have arterial disease since ischaemic changes in the erectile tissues may be an aetiological factor in veno-sinusoidal leakage. Overall, the proportion of patients in this study who were thought to have arterial disease is lower than suggested by previous authors (Virag *et al.*, 1985) despite a similar mean age. This may have been related to our local referral pattern, which appeared to result in the referral of a relatively healthy and active group of patients while, presumably, the majority of patients with known cardiovascular disease were dissuaded from seeking surgical treatment.

In this study arterial inflow to the dependent portion of the penis was measured, without giving consideration to flow in individual vessels. This makes the method less operator-dependent than Doppler methods and ensures that the method remains valid in the presence of normal arterial variability or following revascularisation procedures. The method we have used is a modification of the limb blood flow method of Parkin *et al.* (1986). A feature of the method is that although only flow into the region distal to the cuff is measured, this flow reflects flow in more proximal vessels as there is no possibility of a collateral supply. Thus the method will indicate the presence of haemodynamically significant disease in the more proximal vasculature.

The evaluation of methods for assessing penile arterial supply is hindered by the lack of an accepted standard by which these methods can be compared. Arteriography remains the most definitive investigation but the significance of arterial lesions cannot be assessed because no functional information is gained and vascular abnormality in the smaller vessels is difficult to demonstrate. There is no agreement on the degree of arterial disease, demonstrated on arteriography, that should be regarded as significant in the investigation of impotence. Venous leakage can be demonstrated and measured by cavernosography and cavernosometry but the presence of venous leakage does not exclude arterial disease; indeed the two frequently occurred together in this study and in studies by other authors (Lue *et al.*, 1986). The PBI fails to indicate reliably the presence of arterial disease (Aitchison *et al.*, 1990) because the Doppler signal is often obtained from the dorsal penile artery and this does not correlate with erectile function (Robinson *et al.*, 1989). Flow in the cavernosal arteries, which is more relevant, is difficult to detect without duplex scanning. Duplex scanning has been used to measure changes in individual arterial diameters and peak flow velocity in response to papaverine (Lue *et al.*, 1985) but the method is still under assessment and there is little corroborative evidence to show that the method accurately measures arterial supply. In this study we have used a combination of clinical, arteriographic and cavernosographic evidence by which to classify patients into groups according to the probable underlying aetiology. While such a method may be criticised as being subjective, since clinical judgement often directed the course of investigation, we did not feel that arteriography was justified in all patients, especially those in whom there were no historical or clinical features to indicate arterial disease.

Published studies of penile blood flow in health and disease are extremely rare. Newman and Northup (1981) attempted to study penile blood flow by perfusion studies in cadavers and found that erection could be induced by perfusing the dorsal penile artery at a rate of 25 ml/min. This method failed to take account of the role of venous outflow and of the smooth muscle in the sinusoids of the erectile tissues and was thus a poor model of the situation *in vivo*. Nseyo *et al.* (1984) attempted to assess penile blood flow by the clearance of subcutaneous ^{133}Xe. The theoretical basis of this study was flawed since the authors measured blood flow to the penile skin and failed to appreciate that both the arterial inflow and venous drainage of the erectile bodies are anatomically and functionally largely independent of the penile skin circulation. Fanous *et al.* (1982) attempted to measure penile perfusion from the activity of the penogram following the intravenous injection of radionuclide and assessed the response to intravenous vasodilator. The penile circulation was not isolated during equilibration of radioactivity throughout the body and in addition the injected radionuclide (^{99m}Tc-pertechnetate) was not of a form that was restricted to the intravascular compartment. As a result, the method described, at best, only measured penile volume. A similar study was published by Siraj *et al.* (1986). In this case ^{99m}Tc-RBC was used to label the entire intravascular compartment, and the slope of the time–activity curve, for the penis, was measured before and after the intravenous injection of vasodilator. As in the previous study the change of activity recorded after intravenous vasodilator was related to a change in penile volume. If this were solely a measure of changes in arterial inflow such a study may have been valid but the effect of the vasodilator on venous outflow and cavernosal smooth muscle was not considered.

Penile blood flow in normal volunteers was studied by ^{133}Xe clearance from the corpora cavernosa by Wagner and Uhrenholdt (1980). Flow rates of 2.5–8.0 ml/min were recorded in the flaccid state and this increased to a maximum of 90 ml/min during early detumescence. During established full erection the rate was only 4 ml/min. The clearance method can measure arterial inflow accurately only when there is equilibrium with venous outflow. This is clearly not the case during early erection or during detumescence, when clearance can vary independently of arterial inflow. Nevertheless the study showed that arterial flow is low in established erection and indicates the need to measure flow in the early phase of erection if maximal arterial inflow is to be assessed.

Haden *et al.* (1989), using cavernosal ^{133}Xe clearance, found that there was no significant difference in flaccid state penile blood flow when potent and elderly impotent subjects were compared, suggesting that determination of penile blood flow in the unstimulated state is not helpful in the evaluation of erectile failure. However, the impotent patients were not subdivided according to aetiology in this study and would almost certainly have included patients with veno-sinusoidal leakage in whom one would expect arterial flow to be normal. Our study showed unstimulated flow to be significantly greater in impotent patients without arterial disease compared with impotent patients with arterial disease. This difference could have arisen both from different patient selection and from different technique. Penile ischaemia caused by the inflated cuff in our study may have resulted in reactive hyperaemia which would have been greater in those subjects with a normal arterial supply (Bell *et al.*, 1983). Errors due to this effect were avoided in our study by using the same period of cuff inflation for each measurement but the flaccid state measurements are not comparable to those of other studies without a similar ischaemic period. Despite the significant differences found in unstimulated penile blood flow between patients with and without arterial disease, there was overlap between the groups which rendered this measurement alone too non-specific to be of value in clinical use.

Intracavernous vasodilators such as papaverine and phentolamine have been in clinical use for the investigation of impotence since 1984 (Virag *et al.*) and offer a reliable means of achieving penile smooth muscle relaxation and maximising arterial inflow. The effect requires several minutes to become fully established and in the presence of veno-sinusoidal leakage the drug may be washed out into the systemic circulation and not achieve the desired result. The use of an inflatable cuff in our study ensured that, by isolating the penile circulation, maximal vasodilatation was induced while the penis remained flaccid so that peak arterial flow occurred on deflation of the cuff. The method ensured that the activity increase immediately following cuff release is related only to arterial inflow; during later phases of erection, activity is related to penile volume and this is influenced by multiple factors including arterial inflow, venous outflow, compliance of the erectile bodies and patient build.

We initially anticipated that the ratio of stimulated to unstimulated flow would provide an index by which penile arterial insufficiency could be assessed but the ratio proved unhelpful because of the exceptionally high unstimulated flows in 3 of the patients with veno-sinusoidal leakage (16, 18 and 26). We therefore felt that the unstimulated flow measurement provided no clinically useful additional information and, in the later subjects, we discontinued this part of the assessment and carried out the entire study during a single attendance.

Blood flow measurements after papaverine showed a significantly lower value in those patients with arterial disease. The absence of overlap between the arteriopathic and the non-arteriopathic subjects is of practical importance because a limit of approximately 20 ml/min/100 ml can be used to distinguish the 2 groups. The blood flow measurements in the control subjects and in those with venous leak (in the absence of additional arterial disease) were not significantly different. This is as would be expected if the method was an independent measurement of arterial flow. The distinction between the 2 groups should be possible by the response to papaverine but a small proportion of normal subjects may require nocturnal tumescence studies or cavernosography because of false negative papaverine tests. Additional confirmation that the test is an independent measure of arterial supply was provided by the results of patient 15, who was restudied after penile vein ligation. The similar blood flow results suggested that the test is reproducible and was not influenced by changes in the venous outflow. Further studies are in progress to confirm these findings.

The 3 patients (30–32) who could not be classified on clinical grounds had stimulated penile blood flows near the 20 ml/min/100 ml limit. Patient 30 had venosinusoidal leakage but was strongly suspected of also having arterial disease as a feature of his collagen vascular disease. However, this could not be confirmed, since consent to arteriography was withheld. Patient 31 had a normal arteriogram and slightly excessive venous leakage but had not improved after 2 attempts at vein ligation. The results of such surgery are not uncommonly poor but in this patient only a slight reduction in venous drainage would have been necessary for a favourable result. It has also been suggested that cavernosometric results in this patient's range are a feature of arteriogenic impotence. These findings suggested that his impotence may have been a result of small vessel disease or sclerosis of the erectile tissue. This remains conjectural but would be compatible with the low blood flow result. Patient 32 had no clinical indication of arterial disease and had a normal cavernosogram. This young patient was remarkably anxious, suffering tremor and sweating during the investigations. A false negative papaverine test is well recognised in such anxious patients and may be due to high levels of adrenergic tone (Buvat *et al.*, 1986). In the presence of such antagonism to the effects of papaverine the low blood flow result is not unexpected and indicates that the test is subject to false negative results in such cases. It is possible to overcome this antagonism by the use of larger doses of papaverine or the combined use of papaverine and phentolamine but at a greater risk of inducing priapism in normal patients. To overcome such difficulties we intend to restudy such patients with sequentially increasing doses of vasodilators.

The classification of patient 26 in the venous leak group may be surprising since cavernosography was normal by our criteria. However, following a normal arteriogram and in the absence of any clinical suspicion of an arterial aetiology, penile vein ligation was performed with good effect. This may be reasonably attributed to a favourable placebo response in a subject with impotence of psychological origin and does not necessarily indicate a venous aetiology. However, the restoration of erectile function confirms the absence of significant arterial disease, and the validity of the study, which was designed to detect arteriogenic impotence, was not altered by including such a patient in the venous leak group rather than the normal group.

A potential source of error in the method was the estimation of penile volume, especially where the dependent portion was small. Flaccid penile dimensions are remarkably variable in the same patient over a short period of time, making accurate measurement difficult. We calculated flaccid penile volume by measuring the length of the dorsal surface of the dependent portion and the circumference at the midshaft immediately prior to applying the cuff. The penile blood volume could, in theory, be accurately measured from an isotope penogram but this would entail a further radionuclide injection in order to assess volume in the absence of vasodilators or reactive hyperaemia; errors would still arise due to changes in flaccid penile volume between studies.

Arteriography will still play a role in the investigation of the small proportion of patients who cannot be classified by a combination of clinical features and blood flow measurements and in those suspected of a remediable arterial lesion by this test. However, with increased familiarity with the use of this test it should be possible to assess the majority of patients by a single outpatient study requiring less than 1 h. In addition, the method described may offer an objective measurement by which the results of penile arterial revascularisation could be assessed.

The estimation of penile blood flow by this method takes more time than the simple papaverine test but is otherwise of no greater inconvenience or risk to the patient. The method we have employed uses the scanning equipment of a well equipped imaging department but the images produced by the Gamma camera could be dispensed with and the production of a time–activity curve could be achieved with a scintillation counter, thus avoiding the need for sophisticated imaging equipment.

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Germ Cell Alkaline Phosphatase in Human Seminal Plasma following Vasectomy

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Summary—Germ cell alkaline phosphatase (also termed placental-like alkaline phosphatase or Nagao isoenzyme) was assayed in seminal plasma using monoclonal antibody-based enzyme immunoassays in samples obtained both before and after vasectomy. In all cases, germ cell alkaline phosphatase fell to undetectable levels within 14 days of operation. A fall in seminal plasma germ cell alkaline phosphatase may thus be an early indication of successful vasectomy.

There are 4 major distinct isoenzymic forms of the human alkaline phosphatases: tissue-nonspecific, intestinal, placental and germ cell alkaline phosphatases (previously termed placental-like alkaline phosphatase) (Stigbrand *et al.*, 1982; Millan and Manes, 1988). They can be distinguished on the basis of relative sensitivity to inhibition by certain L-amino acids, heat sensitivity and differential reactivity with monoclonal antibodies (mAbs) (McLaughlin and Johnson, 1984).

Germ cell alkaline phosphatase (GCAP) is found in normal testicular tissue together with trace amounts of placental alkaline phosphatase (PLAP) (McLaughlin *et al.*, 1984). Human ejaculates are known to have alkaline phosphatase activity (Mann and Lutwak-Mann, 1951) and our previous work has quantitated the presence of seminal plasma GCAP in fertile and infertile males (McLaughlin *et al.*, 1986). In cases of azoospermia, due to either an obstructive aetiology or germinal failure, seminal plasma GCAP levels were very low. In subfertile patients, GCAP levels increased in relation to sperm output from the testes, suggesting that GCAP levels in semen may reflect germ cell function and/or access of testicular products into the ejaculate (McLaughlin *et al.*, 1986). This suggested, therefore, that GCAP is cleared from the seminal plasma following vasectomy because its site of production is proximal to the site of the operative obstruction.

The objective of the present study was to monitor the rate of clearance of GCAP from seminal plasma following vasectomy.

Patients and Methods

Five patients referred to a general Urology Unit for consideration of vasectomy were asked to produce 2 semen samples each after 4 days' sexual abstinence prior to the operation, and then a sample every 14 to 28 days thereafter. It was not possible to collect any samples during the first 14 post-operative days. A pre-operative serum sample was taken for hormone estimation and all 5 patients were found to have FSH, LH, testosterone, oestradiol and prolactin levels within normal limits.

Each pre-operative ejaculated specimen was evaluated for sperm density, seminal volume and sperm progressive motility and each patient was considered to have a normal seminal analysis as defined by WHO guidelines. The remaining ejaculate was then centrifuged at 900 g for 10 min and the seminal plasma supernatant stored in aliquots at −20°C until required for batch assay of PLAP and GCAP. No seminal analyses were performed on post-operative samples but all samples were treated in the same way as the pre-operative seminal plasma samples prior to storage. After 3 months, patients' seminal samples were also examined for the presence of spermatozoa and all 5 patients were found to be azoospermic.

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Estimations of PLAP and GCAP were performed by solid-phase enzyme immunoassays based on the murine IgG1 mAbs H317 and H17-E2, together with simultaneous L-leucine sensitivity estimations (McLaughlin *et al.*, 1983, 1984, 1986). The H17-E2 mAb reacts with both PLAP and GCAP and the H317 reacts with PLAP alone; neither reacts with other forms of alkaline phosphatase (McLaughlin *et al.*, 1983; Travers and Bodmer, 1984). The assay has been previously described in detail (McLaughlin *et al.*, 1983, 1984, 1986), but briefly the mAb was immobilised on to micro-ELISA plate wells (Dynatech) through rabbit anti-mouse immunoglobulin (Dakopatts) and then incubated with the seminal plasma sample diluted 2-fold in phosphate-buffered isotonic saline, pH 7.4. Any PLAP or GCAP subsequently bound was estimated by colour change in a phosphatase substrate. The results were expressed in units per litre (u/l) of alkaline phosphatase activity. The limit of sensitivity of the assay was 0.1 u/l, corresponding to 0.2 u/l in the original sample.

Results

The H17-E2-reactive GCAP activity in pre-operative and post-operative semen samples for the 5 patients in this study are shown in the Figure. This enzymic form was L-leucine sensitive and unreactive with the H317 mAb, and hence was GCAP rather than PLAP. There was a wide variation in GCAP levels for the pre-operative seminal plasma samples of the 5 donors (Fig.), an observation reported previously in normospermic patients (McLaughlin *et al.*, 1986). This investigation had also demonstrated that individual patients maintain a relatively constant seminal plasma GCAP level, in contrast to the marked variation between individuals. In the present study, there was no correlation between pre-operative sperm count and seminal plasma GCAP level in these 5 patients. One patient had undetectable GCAP in the H17-E2 immunoassay. In the remaining 4 patients, all GCAP levels dropped from their pre-operative levels of between 0.5 and 3.0 u/l to <0.2 u/l in the first post-vasectomy sample. GCAP levels then remained undetectable throughout the period of study.

Discussion

We have demonstrated that, in 4 of 5 patients, the level of GCAP in the seminal plasma of normospermic men following vasectomy dropped to undetectable levels by the first available sample 14 to 40 days post-operatively. Levels then remained undetectable for a period up to 122 days. The remaining patient did not have detectable pre-operative seminal plasma GCAP in the H17-E2-based GCAP immunoassay. This is consistent with previous data for occasional patients (McLaughlin *et al.*, 1986) and may be due to non-reactivity of this mAb with certain phenotypes of GCAP, as has previously been described for PLAP (McLaughlin *et al.*, 1983).

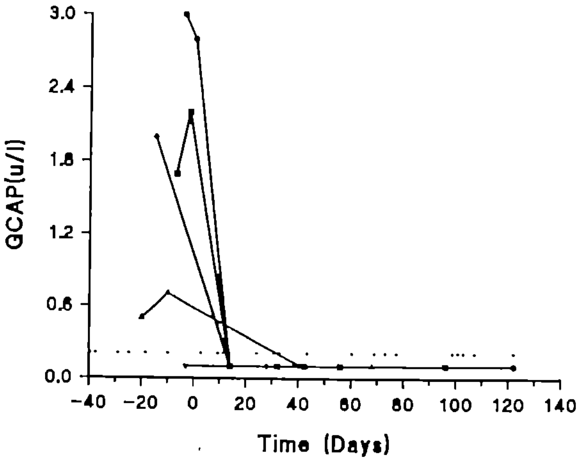

Fig. Seminal plasma GCAP in single samples in individual samples at different times before and after vasectomy. Day 0 = day of vasectomy ..... = limit of sensitivity of assay

These findings are consistent with the majority of this GCAP being produced within the testis, and earlier immunohistochemical studies have demonstrated the expression of GCAP by intratubular cells in the testis which are thought to be of germ cell origin (Paiva *et al.*, 1983). Obstruction of the efferent duct of the testes as a result of vasectomy may prevent access of GCAP into the seminal plasma, and a similar low concentration of GCAP has been reported in the seminal plasma of patients suffering from obstructive azoospermia (McLaughlin *et al.*, 1986).

It is suggested that the measurement of GCAP in the seminal plasma of post-vasectomy patients may act as an early indicator of an unsuccessful operation. Its use as a diagnostic check for infertility after vasectomy is, however, unlikely to replace sperm count. At present, patients have to wait 3 months for complete clearance of sperm from the male reproductive system. Only then can they be certain the operation has been successful.

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Norfloxacin Prophylaxis for Endoscopic Urological Surgery

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Summary—A series of 140 patients, undergoing various types of urological endoscopic procedures, was divided into 2 equal, parallel, randomised groups. The first group of 70 patients, undergoing lower urinary tract surgery, was randomised, half to receive norfloxacin prophylaxis and half no antibiotic cover; the other 70 patients, undergoing percutaneous renal surgery, were randomised, half to receive norfloxacin and half cefuroxime. It was found that 26% of patients not receiving antibiotic prophylaxis and 11% on cefuroxime prophylaxis developed post-operative bacteriuria, with a high incidence of urinary tract infection (UTI). Only 1 patient of 70 on norfloxacin prophylaxis developed post-operative bacteriuria, which quickly responded to prolongation of norfloxacin therapy.

Prior to surgery, 10% of all patients were found to have previously undetected bacteriuria. This group was at high risk of developing post-operative infection. Norfloxacin effectively prevented post-operative bacteriuria and urinary tract infection in these patients. This study suggests that norfloxacin is a safe and effective prophylactic antibiotic in all forms of urological endoscopic procedures.

There is evidence that certain endoscopic urological procedures, notably those involving urethral manipulations as well as endoscopic renal procedures, carry a significant risk of bacterial infection sometimes associated with clinical evidence of urinary tract infection, bacteraemia and even septicaemia. Furthermore, the available data suggest that this morbidity can be reduced by the administration of antibiotics just prior to endoscopic surgery (Shah *et al.*, 1981; Millar *et al.*, 1987; Shearman *et al.*, 1988).

Despite this evidence, many surgeons do not use prophylactic antibiotics in their endoscopic surgery. An important consideration has been the failure of many antibiotics to achieve adequate concentration in the urine and tissues during the period when the patient is at risk of developing urinary tract infection. Norfloxacin, an oral synthetic fluoroquinolone related to nalidixic acid, with a broad spectrum of bacterial activity, is rapidly absorbed and achieves a high concentration in the urine, prostate and seminal fluid.

The aim of this study was to determine the effect of prophylactic oral administration of norfloxacin on the development of urinary tract infection and septicaemia in patients undergoing various types of endoscopic procedures in a busy urological unit.

Patients and Methods

A total of 140 patients entered 2 parallel randomised trials. In Study A, 70 patients undergoing various types of lower urinary tract endoscopic procedures were randomised into 2 equal groups, half receiving norfloxacin prophylaxis and half no antibiotic cover (controls). In Study B, another 70 patients undergoing percutaneous nephrolithotripsy were also randomised into 2 groups, half receiving norfloxacin prophylaxis and half a single intravenous dose of cefuroxime given pre-operatively. In the latter group it was considered unethical not to give some antibiotic cover in view of our previous experience of a case of bacteraemia and septicaemia with this type of surgery.

The dose of norfloxacin was the same in both series, *i.e.* 400 mg (1 tablet) given orally 2 h before

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the procedure and 400 mg *bd* given post-operatively for a total of 6 doses.

Excluded from the trial were children under 12 years, pregnant and nursing mothers, patients with microbiological evidence of urinary tract infection or who were receiving antibacterial therapy for any reason and those with known hypersensitivity to quinolone derivatives.

Urine and blood cultures were taken immediately before and after the procedure and after cessation of therapy. A full aseptic technique was used in all endoscopic procedures. Significant bacteriuria was defined as a count of 10^5 colonies or more per ml of uncentrifuged well mixed urine. Bacteraemia was defined as the presence of viable bacteria in the blood (not necessarily associated with urinary tract infection). Septicaemia was diagnosed on clinical grounds when the patient developed pyrexia and rigors. Statistical analysis was performed using the χ^2 test (using Yates' correction).

Results

In Study A, the endoscopic procedures were similar in both groups, ranging from simple cystoscopy to more complicated transurethral resection procedures (Table 1). Of the 70 patients in the trial (Table 2), 7 patients (10%), including 4 patients in the norfloxacin group, had unrecognised pre-operative bacteriuria and 2 patients (both in the norfloxacin group) had bacteraemia. In the control group 9 patients (26%) developed a post-operative urinary tract infection and 1 developed bacteraemia, whereas none of the patients on norfloxacin prophylaxis developed post-operative bacteriuria/bacteraemia. Those patients who were positive pre-operatively were all cleared of infection by norfloxacin. There were no cases of clinical septicaemia.

In Study B (Table 3), 70 patients undergoing percutaneous nephrolithotripsy were divided into 2 equal groups, half receiving norfloxacin and half cefuroxime prophylaxis as described above. The distribution of patients (with regard to type o stone, sex distribution and length of procedure) was similar in the 2 groups. There were 2 staghorn calculi in each group (all 4 cases with sterile urine pre-operatively). Seven patients (10%) had unrecognised pre-operative bacteriuria (4 in the norfloxacin group) and 4 patients (2 in each group) had bacteraemia. Of the patients treated prophylactically with norfloxacin, only 1 had post-operative bacteriuria (which cleared with an extended dose of the same antibiotic), whereas 4 patients receiving intravenous cefuroxime had post-operative bacteriuria and 2 had bacteraemia, 1 of whom developed septicaemia and renal failure which required dialysis.

Of the 140 patients in the study, 14 (10%) had previously unrecognised pre-operative bacteriuria and 6 (4%) had bacteraemia. All of these patients who did not receive antibiotic prophylaxis developed post-operative UTI. Of the 70 patients (in the combined series) who received norfloxacin prophylaxis only 1 had persistent post-operative bacteriuria (which cleared with a further dose of norfloxacin); this was a significant reduction compared with 26% in patients who did not receive prophylaxis. Moreover, with this dosage regime there were no side effects attributable to norfloxacin therapy.

The bacterial spectrum is shown in Table 4.

Discussion

Many studies (Ball and Powell, 1982; Cafferkey *et al.*, 1982; Hargreave *et al.*, 1982; Millar *et al.*, 1987) have shown a significant risk of bacterial infection following endoscopic manipulation of the urinary tract. It has been suggested that this morbidity can be reduced by the administration of antibiotics just prior to endoscopic surgery (Shah *et al.*, 1981;

Table 1 Endoscopic Procedures in 70 Patients

	No. of patients	*Norfloxacin group (n = 35)*	*Control group (n = 35)*	*Post-operative infection**
Cystoscopy	16	7	9	1
**TUR prostate	27	15	12	4
TUR bladder	10	4	6	3
Urethral dilatation	8	5	3	—
Urethrotomy	6	3	3	2
Ureteroscopy	3	2	1	—
Cystolithotomy	1	—	1	—

* All in the control group; none in the norfloxacin group.
** TUR = Transurethral resection.

Table 2 Infections in Patients Undergoing Endoscopic Procedures

	Norfloxacin group	*Control group*
No. of patients	35	35
Bacteriuria		
pre-op.	4 (11%)	3 (9%)
post-op.	0	9 (26%)*
Bacteraemia		
pre-op.	2 (6%)	0
post-op.	0	1 (3%)
Septicaemia	0	0

* $P < 0.01$

Table 3 Infections in Patients Undergoing Percutaneous Nephrolithotomy

	Norfloxacin group	*Cefuroxime group*
No. of patients	35	35
Bacteriuria		
pre-op.	4 (11%)	3 (9%)
post-op.	1 (3%)	4 (11%)
Bacteraemia		
pre-op.	2 (6%)	2 (6%)
post-op.	0	2 (6%)
Septicaemia	0	1 (3%)

Table 4 Bacteriology of 70 Patients Receiving Norfloxacin Prophylaxis

	Bacteriuria		*Bacteraemia*	
	pre-op.	*post-op.*	*pre-op.*	*post-op.*
Staphylococci	2	0	4	0
Streptococci	0	0	0	0
Gram negative	7	1	1	0
Pseudomonas spp.	1	0	0	0
Propionic bacteria	0	0	1	0

Millar *et al.*, 1987; Murdoch and Badenoch, 1987; Shearman *et al.*, 1988) (Table 5). Most of these studies have been concerned with transurethral resection of the prostate. We have extended the field to include other endoscopic procedures (including percutaneous renal surgery) that are commonly dealt with in a busy urological unit, in an attempt to ascertain whether the use of prophylactic antibiotics (more specifically norfloxacin) is beneficial to the patient and cost-effective.

An important consideration in the prophylactic use of antibiotics is the ability of the drug to achieve an adequate concentration in the prostate, urethra and peri-urethral tissues. Norfloxacin, a synthetic broad-spectrum fluoroquinolone antibacterial agent, is excreted by the kidneys and has been shown to penetrate rapidly to most tissues, reaching a particularly high concentration in the kidneys, bladder and prostate (Bergeron *et al.*, 1985; Holmes *et al.*, 1985). Moreover, it has the advantage of oral administration.

In this study, 10% of patients had a positive urine culture immediately prior to surgery despite previously negative specimens. This is in keeping with other reports (Murphy *et al.*, 1984; Shearman *et al.*, 1988). Others (Morris *et al.*, 1976; Robinson *et al.*, 1982) have shown that patients undergoing endoscopic procedures, particularly TURP, often have viable bacteria in the prostate and urethra despite a sterile urine and that these bacteria often give rise to post-operative urinary tract infections.

Considering these 2 factors it is not surprising that, despite a careful aseptic technique during endoscopic procedures, 26% of our control group developed post-operative bacteriuria and 3% also bacteraemia. A significant reduction in these complications was registered when norfloxacin was given prophylactically to patients undergoing endourethral procedures—none of them showing post-operative bacteriuria. Norfloxacin also appeared to

Table 5 Endoscopic Urological Procedures—Post-operative Urinary Tract Infections

Source	*No. in study*	*Controls (% infected)*	*Prophylaxis (% infected)*	*Antibiotic used*
Shah *et al.* (1981)	200	32	18 10 34	Cephalexin Co-trimoxazole Carfecillin
Millar *et al.* (1987)	179	39	25	Aztreonam
Shearman *et al* (1988)	110	49	11	Ciprofloxacin
Murdoch and Badenoch (1987)	33	36	0	Ciprofloxacin
Cutajar (*present series*)	70	26	0	Norfloxacin

be at least as effective as cefuroxime in patients undergoing percutaneous nephrolithotomy.

Bacteriuria, urinary tract infection and septicaemia may have serious effects both in terms of clinical morbidity as well as from the financial aspect of therapy. Hargreave *et al.* (1982) showed that a short course of a safe antibiotic is cost-effective for TURP. The present series suggests that this is true for most endoscopic procedures commonly carried out in a urology unit, including percutaneous renal surgery. In our experience a course of 6 doses of norfloxacin appears to be safe and effective. Whether a single dose of this drug is just as effective is the subject of further trials. It is our present policy to cover all, except simple cystoscopic examinations, with a prophylactic dose of norfloxacin.

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PAEDIATRIC UROLOGY

Laser Treatment of Posterior Urethral Valves in Neonates

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Summary—The posterior valves of 13 neonates were resected using the neodymium:YAG laser in retrograde transurethral endoscopy. There were no strictures or other complications.

Posterior urethral valves in neonates have been managed in a number of ways (Engelskirchen and Gharib, 1990). The neodymium:YAG laser has been used successfully to treat older children via the transvesical route (Ehrlich *et al.*, 1987). We present the retrograde, transurethral application of this laser in neonates.

Patients and Methods

Thirteen children aged between 2 days and 4 weeks (mean 9 days) underwent retrograde transurethral laser resection of posterior urethral valves (Fig. 1).

Eleven children received Young I valves and 2 received Young III valves. In 4 children the diagnosis had been established antenatally. Of those known to have urethral obstruction only after birth, 2 developed urosepsis. As soon as the tentative diagnosis had been made and metabolic balance achieved, a suprapubic catheter was inserted and intravenous urography and voiding-cystourethrography (VCU) were performed. This was followed by endoscopy with laser resection. Transurethral catheters were seldom used pre-operatively.

Cystoscopy was performed under general anaesthesia and in the lithotomy position using a Storz No. 8 cystoscope. The valves were exposed. The 600 μm bare fibre was introduced through the side channel and brought into contact with the central portion of the valves, which were then vaporised, advancing centrifugally (Fig. 2).

The maximum power setting was 25 watts for a maximum of 0.2 s with intervals of 0.3 s. The valves were not completely removed. Small marginal fins were left to undergo spontaneous shrinkage (Fig. 3).

Cystoscopy was performed, including probing of the ostia of both ureters. A 4 F catheter without a balloon was inserted for 5 days, allowing voiding around the tube. The children were discharged and followed up on an out-patient basis. After 4 weeks a VCU was obtained (Fig. 4). Follow-up extended from 6 months to 5 years (mean 2.3 years).

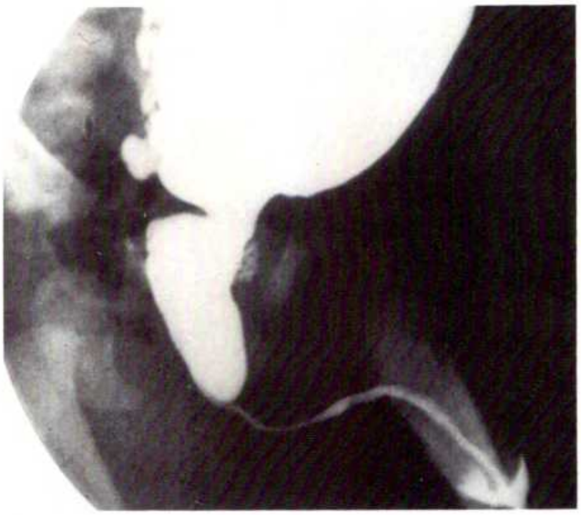

Fig. 1 Typical 2-day-old child with posterior valves (Young I).

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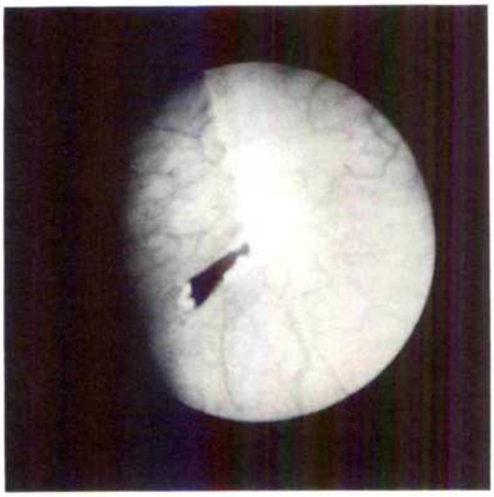

Fig. 2 Same child, endoscopic view. The central perforation has already been widened. The tip of the bare fibre is visible in the centre.

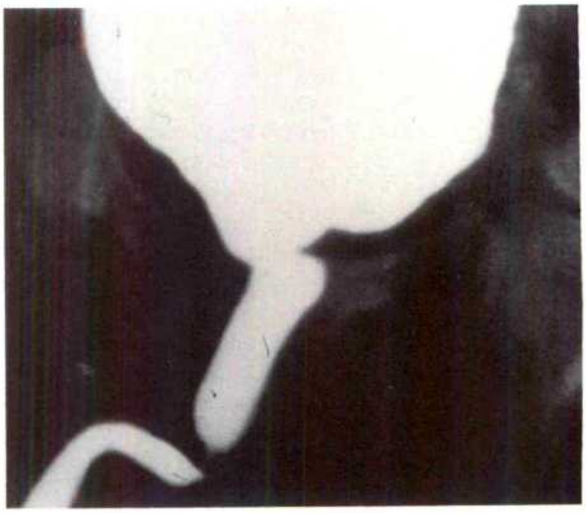

Fig. 4 Same child 1 month after laser resection. No stricture.

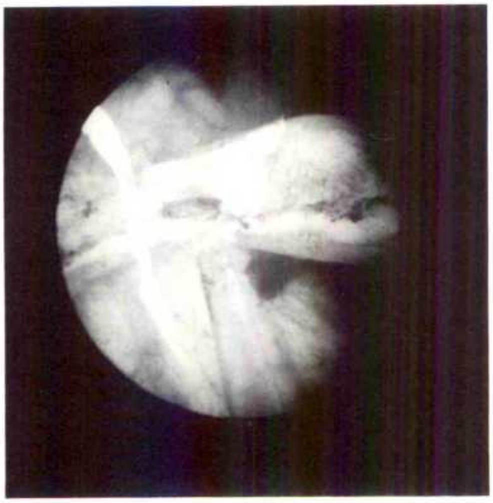

Fig. 3 The base of the valve has been left for spontaneous shrinkage (lateral view on to the urethral wall).

Results

No strictures were observed. One child had to undergo laser endoscopy for a second time 3 days after the initial procedure and has since remained free of recurrences. In this child the first endoscopy had been technically complicated and resection was therefore incomplete. Incontinence was not reported. Six children still had vesicoureteric reflux (grade IV) at the ages of 2 to 5 months. This was treated surgically in 4 cases and in the other 2 it improved spontaneously. The 4 children operated on for reflux underwent cystoscopy on that occasion. No trace of the resection, especially the residual valves, could be detected in any of them. The 7 remaining children had megaureters and regular sonography revealed slight improvement rather than deterioration. The 2 children in whom severe obstruction had been diagnosed antenatally were among the 4 who had antireflux procedures and they will probably require dialysis in the future. None of the children had kidney transplants.

Discussion

The No. 8 cystoscope allows endoscopy of the urethra and bladder in neonates. The neodymium: YAG laser beam can be transmitted by advancing the 600 μm bare fibre through the side channel of the cystoscope. Retrograde endoscopic laser application in the neonate is thus technically feasible without causing undue trauma. In view of the technical standard of the equipment, supravesical diversion—which carries its own risks—no longer seems justified as the primary step (Krueger *et al.*, 1980). The policy of initially performing a cutaneous vesicostomy (Ehrlich *et al.*, 1987), or some other form of diversion, and then waiting 1 year for ablation of the valves, was dictated by the fact that instruments were too large to allow intervention before the organs had reached a certain size. We are unable to identify any long-term benefit from this procedure and indeed the contrary seems to be true (Pompino *et al.*, 1990). The earlier the valves are removed, the fewer the number of secondary interventions that are required in the proximal urinary tract and subsequent nephrectomies (Engelskirchen and Gharib, 1990). In addition, the bladder should be allowed to resume its normal function as soon as possible: once the normal structure is restored, vesicoureteric reflux will often subside and kidney function will not deteriorate further (King, 1985).

In previous attempts to remove urethral strictures, two-thirds of adult patients suffered recurrent strictures within 1 year (Smith and Dixon, 1984). Although not fully comparable with the situation in the valves of neonates, these results stress the technical aspects of the procedure. In these cases, the high power settings and long duration of laser irradiation may have contributed to post-operative scarring, eventually leading to new strictures. The settings we found useful (maximum 25 watts for 0.2 s at intervals of 0.3 s) created fewer changes in the surrounding tissue than 40 to 45 watts and 3–5 s. Limiting the pulse duration permits the underlying tissue to spread thermal energy during pauses, thus limiting the depth of tissue affected by the laser. Pulse durations <0.2 s also greatly reduce the possibility of self-destruction of the fibre tip (Berlien *et al.*, 1990a). The tip of the fibre applied directly to the valves leads to a well defined, homogeneous zone of carbonisation within which the laser beam couples. This results in instant vaporisation even at low power settings (Berlien *et al.*, 1990b). Also, visual control of the laser is difficult under water. While the laser beam is strongly reflected in air, it penetrates to a significantly higher degree under water. Furthermore, the tissue is cooled continuously. Effects at deeper levels may be much greater than is evident from observing the surface. Thus we always left the marginal base of the valves intact.

Sapphire tips, which are used to treat urethral strictures in adults, cannot be used in children because they are too large to be passed through infant cystoscopes. The results have been found to be superior (Shanberg, 1984), or at least identical, to those obtained with a cold knife incision (Smith, 1989). The smallest resectoscopes available for children, however, have a diameter of 10 F and are thus not suitable for neonates.

The valves do not have to be removed flush with the surface of the urethra. Attempts to be too thorough can only lead to injury to the underlying tissue and to failure. As long as the laser beam is applied parallel with the urethral wall, the risk of penetration is low. This has been confirmed by the results of endoureteric laser application in treating cancer of the ureter in adults. Here too, no perforations have been reported (Schilling and Böwering, 1985).

As in other areas of paediatric surgery, long-term results are not yet available. It has been suggested that the number of adverse results will increase from decade to decade (Parkhouse, 1988) and careful follow-up is mandatory. Nevertheless, it seems advisable to commence treatment early, to rely on normal physiology and to strive for a good balance between over- and under-treatment.

Endoscopic laser resection of urethral valves is not technically difficult. It is fast and efficient, and we consider it to be the least traumatic procedure.

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British Journal of Urology (1992), **69**, 428–429

Skin Chordee without Hypospadias—an Under-recognised Entity

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Summary—Skin chordee is a congenital abnormality due to failure of development of the mesenchyme surrounding the primitive urethra. It is frequently misdiagnosed as hypospadias. We describe the presentation and surgical management of 12 patients who presented to this hospital over the past 3 years.

Chordee usually occurs with hypospadias and results in abnormal curvature of the penis. Chordee may present, however, with the urethral meatus located in its normal position on the glans penis. Three types of chordee without hypospadias have been described (Devine and Horton, 1973). Type I is the most severe, the corpus spongiosum being deficient from the site of the start of the chordee to the glans penis. In Type II the urethra is surrounded by normal corpus spongiosum but Buck's fascia and the dartos layers are abnormal. In Type III the abnormal dartos layer tethers the skin to the corpus spongiosum and Buck's fascia, resulting in skin chordee without hypospadias. Type III is thought to be rare, but we describe 12 patients presenting over a 3-year period and suggest it is more common than previously noted.

Embryology

The urethra forms on the dorsal surface of the genital tubercle from a flat plate of cells which become grooved until the edges of the groove fuse to form a tube. The developing mesenchyme then surrounds the urethra first with the spongiosum tissue, then Buck's fascia and finally the dartos layers. An early interruption in this process results in a Type I case and a later interruption causes skin chordee. Kaplan and Lamm (1975), in a study of 46 fetuses, suggested that chordee is a normal stage in penile embryogenesis and chordee may persist well into the third trimester of gestation.

Patients and Methods

Twelve boys with skin chordee without hypospadias presented between January 1987 and January 1990. Their age at presentation ranged from 6 months to 3 years (mean 2.2 years). Ten were misdiagnosed by the referring doctor as suffering from hypospadias, but the urethral meatus was terminal in all cases once the hooded foreskin had been retracted. The chordee resulted in a ventral curvature in all cases and the median raphe was deviated in 4 with minor degrees of penile torsion. A hooded foreskin was present and normal corporal bodies were palpable in all cases. There were no other associated urological abnormalities.

Procedure

The patients were placed in the supine position and all procedures were performed under general anaesthesia. The degree of chordee was assessed. The amount of excess dorsal foreskin was measured and the terminal position of the meatus confirmed. The foreskin immediately proximal to the glans was circumcised, starting lateral to each edge of the urethra. In 3 cases the ventral covering of the terminal urethra was relatively thin and great care was required in dissection. The penis was degloved down to its base and the tight abnormal dartos adhesions holding the skin to Buck's fascia on the ventral surface were divided. In 3 cases an artificial

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erection was performed to confirm that chordee was limited to skin. Because the chordee results in part from lack of skin on the ventral surface of the penis, Byar flaps were fashioned from the excess of hooded foreskin and wrapped around the ventral side. This resulted in abolition of the chordee and satisfactory apparent lengthening of the penis. A catheter (feeding tube) was placed in the urethra in 7 children for 24 to 28 h.

Results

All patients were examined before discharge after 24 to 28 h and re-examined 6 weeks post-operatively. A satisfactory cosmetic result was noted in all cases. An improvement in direction of flow was noted in the older children.

Discussion

True skin chordee is a milder condition than either Types I or II chordee without hypospadias and can always be repaired without dividing the urethra and producing an iatrogenic hypospadias.

Unlike Devine and Horton (1973), who stated that the foreskin was not hooded in those cases with a terminal meatus, we found that all of the children in this series had both a terminal meatus and a hooded foreskin. In addition, we found that making a circumferential incision and fully degloving the penis, as described by Allen and Spence (1968), was a more straightforward procedure than the vertical incision and subsequent Z-plasty described by Devine and Horton (1973). Another approach to the problem of chordee without hypospadias is to avoid ventral dissection and to excise wedges of the fascia from the dorsal aspect of the penis (Nesbit, 1967). Only 3 boys in this series had an artificial erection test, which did not show any underlying abnormality. When dealing with children with chordee or suspected penile deformity, all should be tested before any correction is performed. It is important to stress that 10 of our patients were referred as having hypospadias, probably due to the presence of a hooded foreskin, which is associated with hypospadias. This has important implications for the parents of these children who had, in several cases, been prepared for a more lengthy and possibly more difficult post-operative course than proved to be the case.

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Case Reports

Stone Formation on a Self-expanding Metallic Stent

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The use of self-expanding metallic stents in the treatment of men presenting with retention of urine has been described by McLoughlin *et al.* (1990). These stents are designed to permit epithelialisation, thus minimising the risk of encrustation and stone formation.

Case Report

An 80-year-old man presented with chronic retention of urine. This was managed initially by a period of indwelling urethral catheterisation which allowed resolution of the uropathy. After insertion of a stent the patient failed to void and required suprapubic catheterisation for 8 weeks. A second device was then inserted and this allowed him to resume spontaneous micturition. During the early follow-up period the patient was noted to have asymptomatic bacteriuria on several occasions but this was not treated as it was hoped that spontaneous resolution would occur following epithelialisation of the stent. Thirteen months after insertion of the initial stent he presented with frank haematuria and investigations revealed a large intravesical calculus straddling the proximal end of the stent across the bladder neck (Fig.). At endoscopy the stent was noted to be epithelialised apart from a small area at the bladder neck. The stone was dislodged into the bladder and disintegrated under direct vision, using an endoscopic lithotriptor, prior to evacuation of fragments with an Ehlichs. Following this procedure the patient voided spontaneously. In view of the previous episodes of bacteriuria he was placed on long-term prophylactic antibiotics.

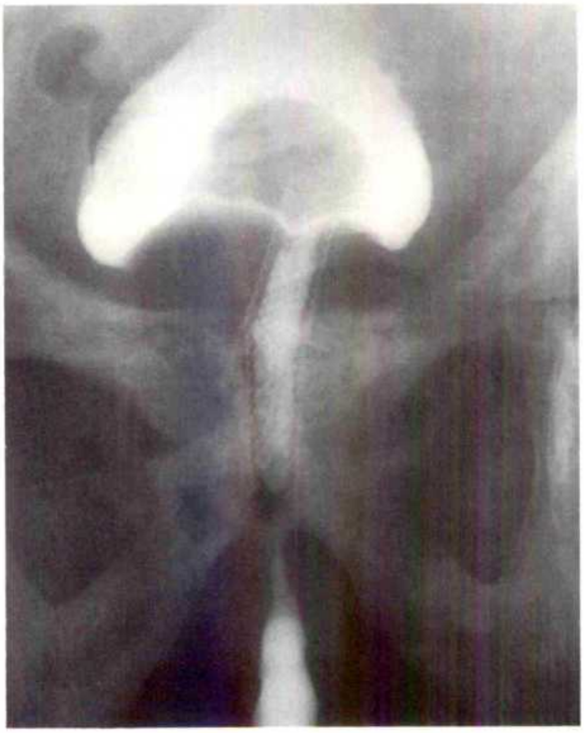

Fig. Stone formation on a self-expanding prostatic stent.

Comment

These stents are completely epithelialised by 6 months in the majority of men. A risk of stone formation remains, however, should the proximal end of the stent lie proud of the bladder neck or should there be persistent bacteriuria.

Reference

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Endometriosis of the Ureter

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Intrinsic ureteric involvement by endometriosis is rare. We present a case in a post-menopausal woman where it mimicked transitional cell carcinoma.

Case Report

A 58-year-old woman complained of abdominal pain and an ultrasound scan showed a left-sided hydronephrosis. Antegrade and retrograde pyelography showed an apparent intrinsic ureteric obstruction 3 cm above the bladder (Fig. 1).

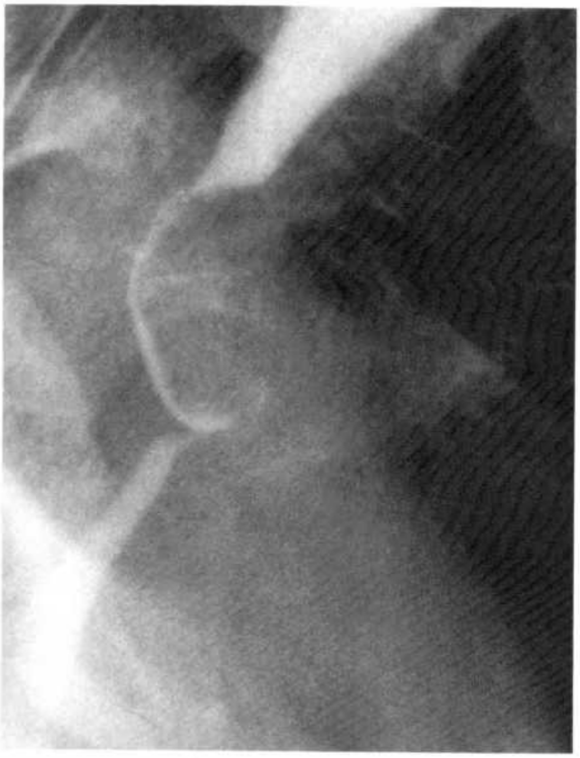

Fig. 1 Lower end of left ureter: antegrade pyelogram, oblique view.

At the age of 42 the patient underwent a total hysterectomy and bilateral salpingo-oophorectomy for endometriosis which involved the bladder. She received regular oestradiol implants up to the age of 50, when she had a Hartmann's operation for presumed obstructing carcinoma of the rectum. However, histology showed this to be due to intrinsic rectal endometriosis.

The current ureteric obstruction was treated by a conservative lower ureterectomy and ureteroneocystostomy after intra-operative frozen section had confirmed intrinsic ureteric endometriosis. Paraffin sections demonstrated endometriotic cystic changes, with endometriotic tissue present in the ureteric muscularis (Fig. 2).

Comment

Endometriosis of the ureter is rare; extrinsic involvement is 4 times more common than intrinsic involvement, as seen in this patient (Shook and Nyberg, 1988). Ureteric endometriosis has a serious morbidity rate, with a kidney salvage rate of only 25% (Moore *et al.*, 1979).

This case is noteworthy because oestradiol implants had maintained an endometriotic focus despite bilateral oophorectomy 17 years previously.

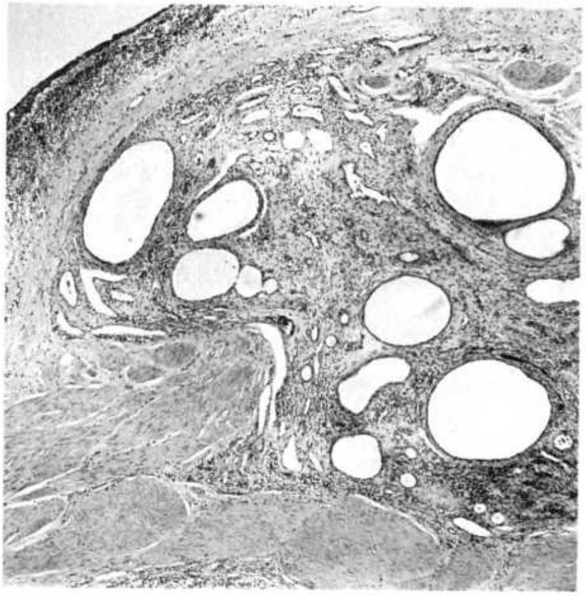

Fig. 2 Endometriosis in the ureteric wall. (H and E × 5).

The patient's previous rectal endometriosis had also mimicked carcinoma but intra-operative frozen section on this occasion confirmed ureteric endometriosis; this avoided excision of the intramural ureter and a bladder cuff.

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Urethral Amyloid

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Case Report

R.N.H., a 42-year-old male Caucasian, presented in April 1988 with urethral bleeding on 4 occasions over the preceding 2 years. He had had 1 episode of haematuria

12 months before which had settled spontaneously but he had felt unwell intermittently thereafter, although his appetite remained good and he had not lost weight. There were no positive findings on general examination and his genitalia were normal. Cytological examination of urine showed no malignant cells and an intravenous urogram was normal. Panendoscopy revealed a soft irregular circumferential mucosal lesion about 1.5 cm long in the mid-penile urethra, which was biopsied (Fig. 1). The rest of the urethra was normal. Histology showed subepithelial amorphous eosinophilic material with positive staining for amyloid and no associated inflammation (Fig. 2). Subsequent rectal biopsies showed no amyloid. Serum electrophoresis was normal and early morning urine samples were negative for Bence-Jones protein. The urethral amyloid was confirmed to be non-AA type on the basis of resistance to oxidation by potassium permanganate and is most likely to be AL type. No specific treatment was undertaken and at follow-up 6 months later he reported that the bleeding had not recurred.

Comment

The urethra is an uncommon site for localised genitourinary amyloid. Amyloid within the urinary tract usually presents with bleeding (Fujihara and Glenner, 1981), though in a few cases it presents with obstruction, as a mass or as a filling defect on intravenous urography (Fox *et al.*, 1984) indistinguishable from a neoplasm. With negative urine cytology, amyloid should be considered in tumour-like lesions and its presence excluded by biopsy. Persistent bleeding in our patient would have required resection of the lesion. Plasma cell dyscrasias which may be associated with AL amyloid were excluded and there was no history of gonococcal urethritis (Walter *et al.*, 1983), indicating that this was a case of localised idiopathic urethral amyloid.

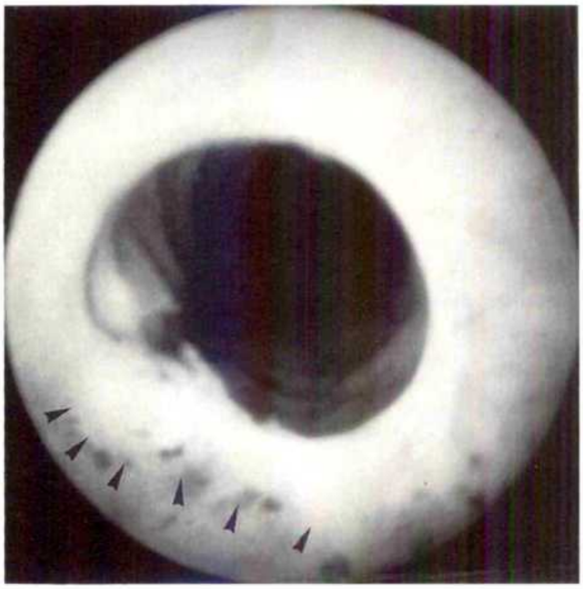

Fig. 1 Endoscopic view of lesion (arrows).

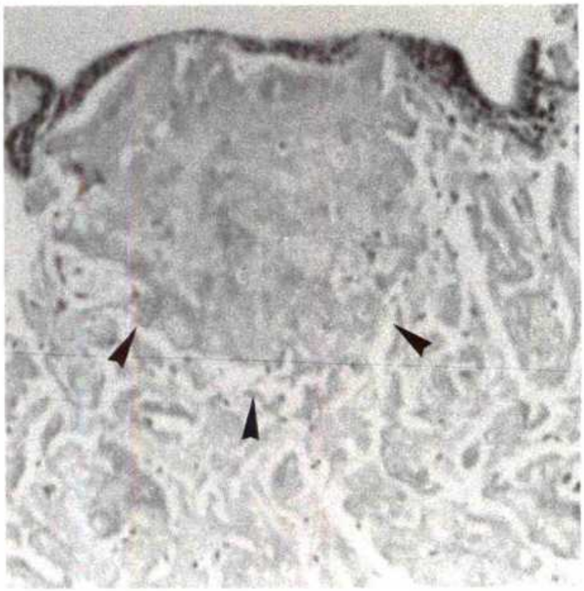

Fig. 2 Superficial urethral wall showing amyloid (arrows) (The stain is sirius red. Magnification × 125).

Acknowledgement

We thank Dr A. G. McIver for help with the preparation of this case report.

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Cystine Stones Treated by Percutaneous Ultrasonic Lithotripsy

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Cystine stones are a rare type of stone found in the urinary tract. We present 2 patients with cystine stones.

Case Reports

Case 1. A 14-year-old Malay female presented with a 2-week history of right ureteric colic associated with fever and haematuria. Plain abdominal X-rays showed a left renal staghorn calculus (Fig. 1) and subsequent investigations revealed a radiolucent stone in the right lower ureter. Initial studies showed normal calcium and uric acid levels and normal renal function. She underwent a left percutaneous ultrasonic lithotripsy (PUL) and a right ureterolithotomy was also performed after failure to retrieve the stone by endoscopic methods.

Three months post-operatively she developed a left renal calculus. Extracorporeal shockwave lithotripsy failed to fragment the stone and a second PUL was performed. Six months later she developed a recurrent stone.

Subsequent metabolic studies revealed cystinuria and she was referred for medical treatment. She was placed on a high fluid intake of 4 l, the urine was alkalinised with sodium bicarbonate and mercapto-propionyglycine was started in view of recurrent stone formation. There was no family history of similar problems.

Case 2. A 32-year-old Chinese male presented with a 30-year history of bilateral renal stones. He had undergone open surgery when aged 2 and 20 years.

Apart from a slightly raised creatinine level (151 µm; normal 120 µm), calcium, urates and electrolytes were normal. Intravenous urography revealed bilateral staghorn calculi with dilatation of the collecting system on both sides (Fig. 2).

He underwent bilateral PUL over a period of 3 months, and this was successful in clearing the stones. Six months later a right renal stone recurred which failed to respond to 3 sessions of extracorporeal shock wave lithotripsy (ESWL). PUL was repeated but 3 months later he developed a further renal calculus and the stone from the previous PUL was found to contain cystine. He was then lost to follow-up.

Comment

Cystine stones in the urinary tract are rare (Caldwell *et al.*, 1978). Cystinuria is due to a genetic defect in the tubular reabsorption of dibasic amino acids. Cystine is the least soluble and tends to precipitate out; 63% of cystinuric patients present with calculus disease, usually by the age of 25 years (Dahlberg *et al.*, 1977).

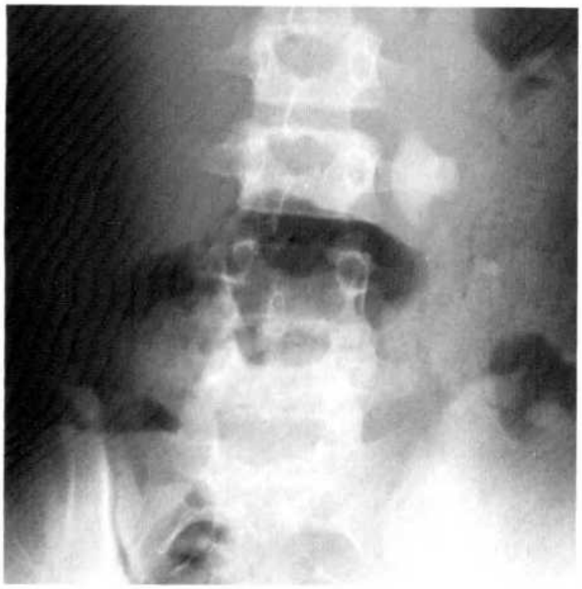

Fig. 1

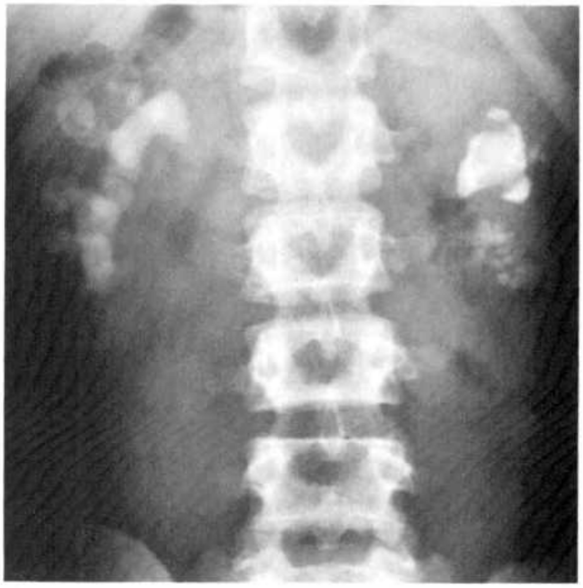

Fig. 2

The initial management of such stones should be medical and consist of a high fluid intake, alkalinisation of the urine and administration of drugs such as D-penicillamine and N-acetylcysteine.

Surgery plays a major role in the management of cystinuric patients with obstructive uropathy and infection. Open surgery is best avoided, since the patients are often young and tend to form recurrent stones. ESWL is unsuccessful as cystine stones tend to be hard in consistency. PUL with antegrade ureteroscopic ultrasound lithotripsy should be considered as the first choice for upper tract stones because it can be done repeatedly with minimal morbidity. It has a better success rate in clearing upper tract stones because it gives a direct view of the stone and can disintegrate the hard cystine stones prior to manual removal. Lower tract stones are best approached by retrograde ureteroscopy, after which they can be fragmented by ultrasonic lithotripsy.

Antegrade nephrostomy puncture with the application of various reagents has been advocated to dissolve the stones but has the disadvantage of being less predictable, involves a longer stay in hospital and produces various side effects (Burns and Hamrick, 1986).

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Urethral Foreign Body

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Foreign bodies in the urethra seldom cause retention of urine. We present a case where a normal, healthy male introduced an object into the urethra to relieve an itching sensation.

Case Report

A 40-year-old man was admittted with retention of urine with overflow, haematuria and dysuria. He gave a history of scratching his urethra with a rubber object. X-ray of the urethra and bladder revealed a foreign body in the urethra extending into the bladder. While in hospital the patient suddenly experienced complete relief of symptoms as the object slipped back into the bladder. Following cystoscopy the foreign body was removed and found to be a long, thick (18F) rubber ring which was cut at one point (Fig.).

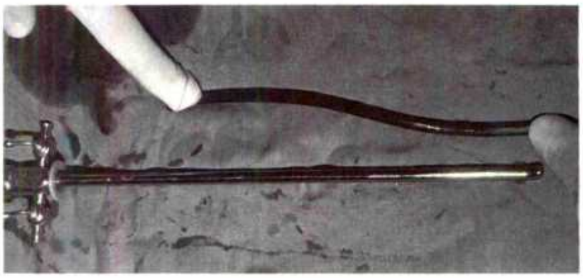

Fig.

Comment

Urethral foreign bodies are uncommon and vary from small pins to large needles, pencils, hair clips, thermometers, *etc*. Patients tend to seek treatment late, especially if the object does not cause symptoms. The problem is common in psychiatric patients, when the situation can be repetitive (Kenney, 1988), but some normal patients use it for sexual gratification. Urethral itching, which is a rare but well documented cause of this problem (Franzblau, 1973), led our patient to insert the object.

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Malignant Fibrous Histiocytoma of the Renal Capsule

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Case Report

A 49-year-old female discovered a tumour in her abdomen shortly before being admitted to hospital. Her previous history was uneventful.

Examination revealed a mobile, large, hard tumour in the right hypogastric region. Haematological and biochemical tests, chest X-ray and bone scan showed no abnormalities. Intravenous urography showed normal structures on the left side but on the right only the upper calices appeared normal. The rest of the renal pelvis was obscured by a 12-cm tumour. Sonography identified a 9 × 12 cm tumour, partly filled with liquid, originating from the lower pole of the right kidney, and a 1.5 cm lesion in the left hepatic lobe. Computed tomography confirmed the haemangioma of the liver and a solid tumour with central necrosis and cranial displacement of the kidney. Angiography showed the lesion in the kidney to have a pathological vessel pattern and non-homogeneous filling during the parenchymal phase (Fig. 1). Suspecting a renal carcinoma, we performed a transperitoneal nephrectomy. The patient made an uneventful recovery.

Macroscopic inspection showed the right kidney to be small. The tumour appeared to originate from the capsule of the lower pole. It was surrounded by smooth connective tissue, displayed a greyish-white cut surface and contained central necrosis or haematoma (Fig. 2).

Histological examination showed spindle-shaped nuclei of fibroblastoid cells embedded in collagenous stroma. Interspersed were groups of histiocytes and pleomorphic giant cells with large nuclei and moderate mitotic activity. In several sections the tumour cells lay only a few tissue layers from the capsule. Stain for alpha-1-antichymotrypsin was moderately positive in the tumour cells but stains for desmin and actin as a pure muscle marker proved negative.

Comment

Approximately 12 to 14% of malignant fibrous histiocytomas occur in the retroperitoneum or kidneys. Only 6 cases originating in the renal capsule have been described (Takashi *et al.*, 1987). The most common symptoms are a palpable abdominal tumour, fever, fatigue, weight loss and gastrointestinal problems (Kearney *et al.*, 1980). The diagnosis can only be made histologically.

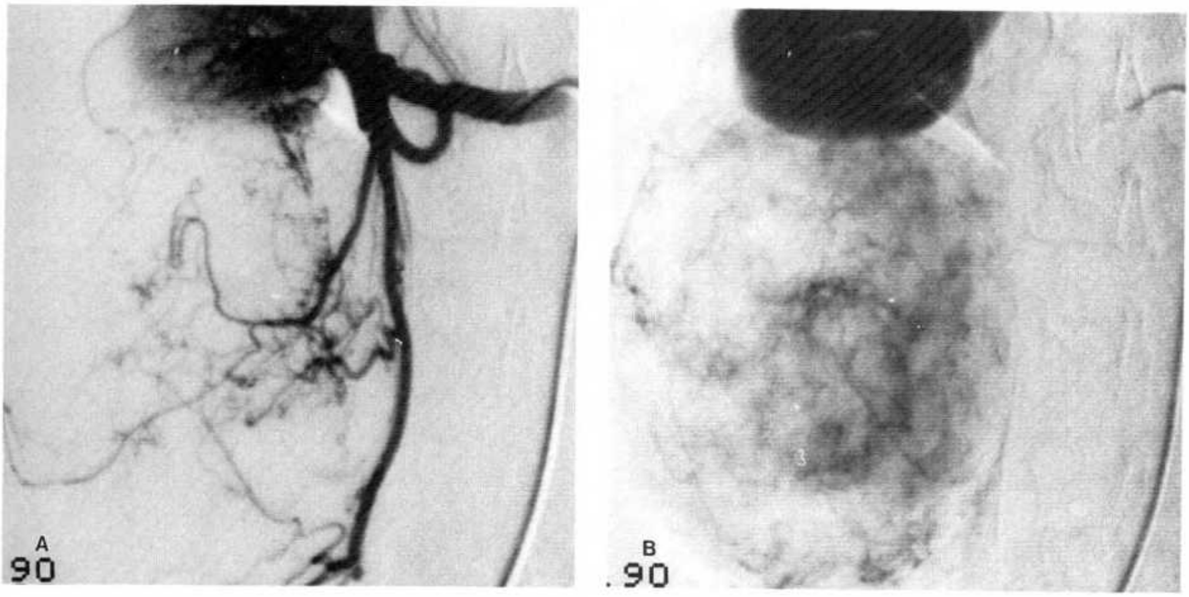

Fig. 1 Selective digital substraction angiogram of right kidney shows (A) a large mass with pathological neovascularity in the arterial phase and (B) non-homogeneous filling in the parenchymal phase.

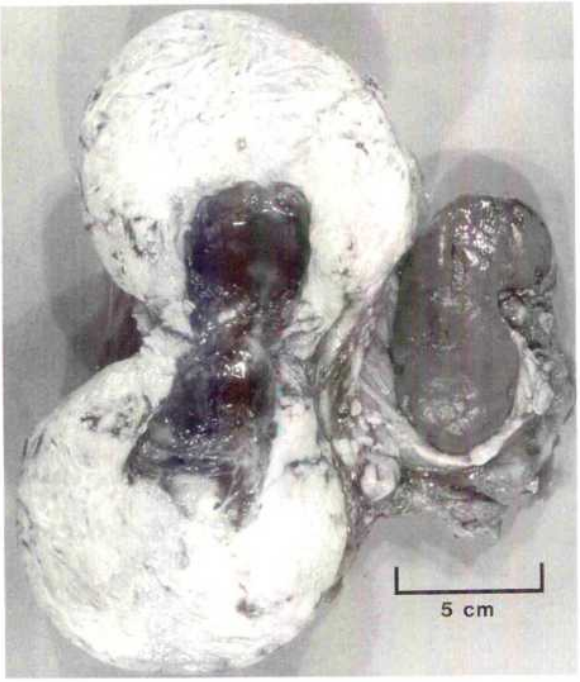

Fig. 2 Gross appearance and cut surface of the tumour, which appears as a greyish-white mass with central necrosis; it is partially detached from the renal parenchyma.

The best treatment is radical removal of the tumour. If there is local infiltration or distant metastases, treatment with cyclophosphamide, vincristine, doxorubicin, actinomycin D or cisplatin may be indicated, although the response rate is only 33% compared with other sarcomas (Leite *et al.*, 1977). Radiotherapy offers little, if any, benefit. The overall prognosis is poor and the 5-year survival rate is less than 14% (Kearney *et al.*, 1980).

References

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Leite, C., Goodwin, J. W., Sinkovics, J. G. *et al.* (1977). Chemotherapy of malignant fibrous histiocytoma. A Southwest Oncology Group report. *Cancer*, **40**, 2010–2014.

Takahashi, M., Murase, T., Kato, K. *et al.* (1987). Malignant fibrous histiocytoma arising from the renal capsule: report of a case. *Urol. Int.*, **42**, 227–230.

Requests for reprints to: J. A. Schneider, Department of Urology, General Hospital of Ingolstadt, Krumenauerstrasse 25, 8070 Ingolstadt, Germany.

Primary Hepatorenal Hydatid Disease

K. RADHAKRISHNA, P. L. N. G. RAO and V. SHENOY,
Departments of Paediatric Surgery and Paediatrics, Kasturba Medical College and Hospital, Manipal, India

Case Report

A 9-year-old boy was admitted with a 4-week history of abdominal pain and fever. He had had similar attacks previously and had been in close contact with a pet dog.

Examination revealed 2 abdominal masses, one in the left epigastric region and the other in the left lumbar region. Both were cystic, with doubtful cross-fluctuation. A dumb-bell mesenteric cyst was diagnosed. Sonography revealed 2 separate cystic masses, one in the left lobe of the liver and the other in close relation to the left kidney. Intravenous urography showed medial displacement and distortion of the left pelvicaliceal system (Fig. 1). Casoni's test was negative. A laparotomy was performed and hydatidosis was diagnosed. The first hydatid cyst was in the left lobe of the liver and was about to rupture, and the second was in the cortex of the left kidney (Fig. 2). There were no daughter cysts and the peritoneal cavity was free. The ectocysts were removed and the cavities obliterated. The patient made an uneventful recovery and intravenous

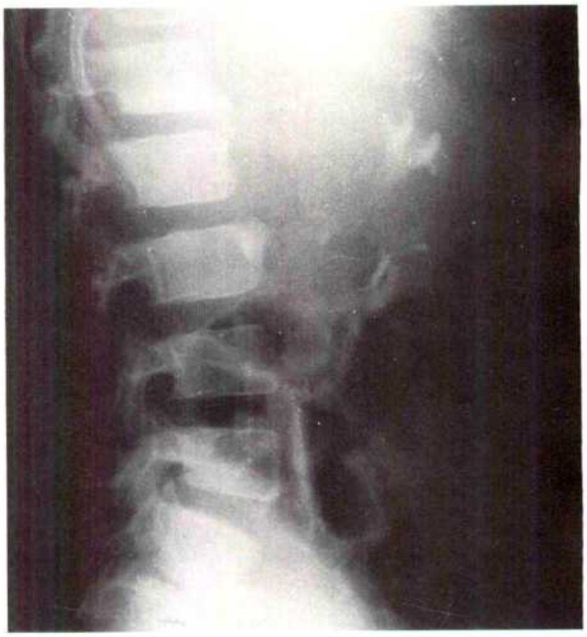

Fig. 1 Intravenous urogram (lateral view) showing anteriorly displaced and distorted left pelvicaliceal system.

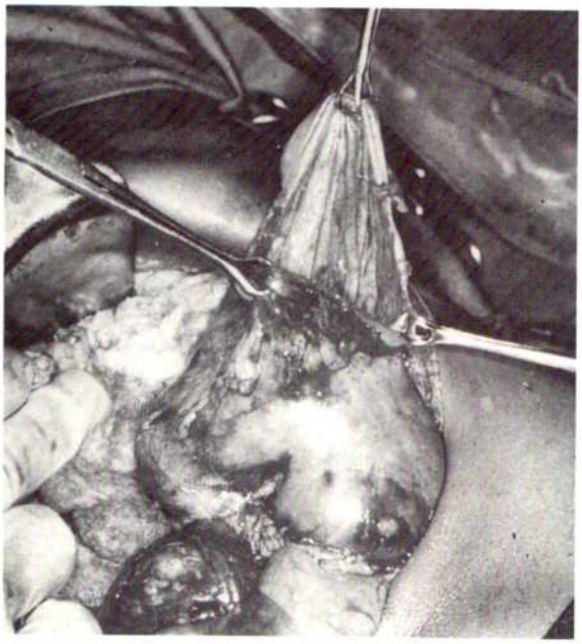

Fig. 2 Left kidney following removal of the ectocyst.

urography showed a normal left pelvicaliceal system. Other members of the family were screened by sonography and were found to be normal.

Comment

Renal involvement in hydatid disease is isolated (Smile *et al.*, 1990) and rarely a part of multi-organ involvement (Mauhoob *et al.*, 1987). While hydatid disease often affects both the liver and the lungs, hepatic and renal involvement without evidence of pulmonary or peritoneal involvement is rare. Kirkland (1966) stated that enucleation of renal hydatid cysts is seldom feasible but we have not found this to be so.

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Smile, S. R., Bose, S. J. C. and Sibal, R. N. (1990). Giant hydatid cyst of the kidney (a case report). *Indian J. Surg.*, **52**, 111–112.

Requests for reprints to: K. Radhakrishna, Department of Paediatric Surgery, Kasturba Medical College and Hospital, Maipal 576119, South India.

Pilonidal Abscess of the Penis

A. B. KHAN and R. N. SCOTT, *Department of Surgery, Hairmyres Hospital, East Kilbride*

Case Report

A 46-year-old man presented with a 2-week history of pain and gross swelling of his penis. On examination there was a severe balanitis with a pointing abscess of the foreskin. At operation a dorsal slit was performed, revealing a collection of pus within the tissues of the foreskin. This was associated with an underlying pilonidal sinus containing human hair related to the coronal sulcus (Fig). The foreskin was trimmed to allow drainage of the abscess and excision of the sinus. Regular dressings were applied until healing had occurred, and circumcision was performed 6 months later. He has had no recurrence of his pilonidal abscess after 2 years.

Comment

Pilonidal sinus occurs most commonly in the sacrococcygeal area and 6 cases of pilonidal sinus of the penis have been reported (Fisher *et al.*, 1976; Goudarzi and McColl, 1976). All of these patients presented with a long history and were either treated conservatively or underwent repeated sur-

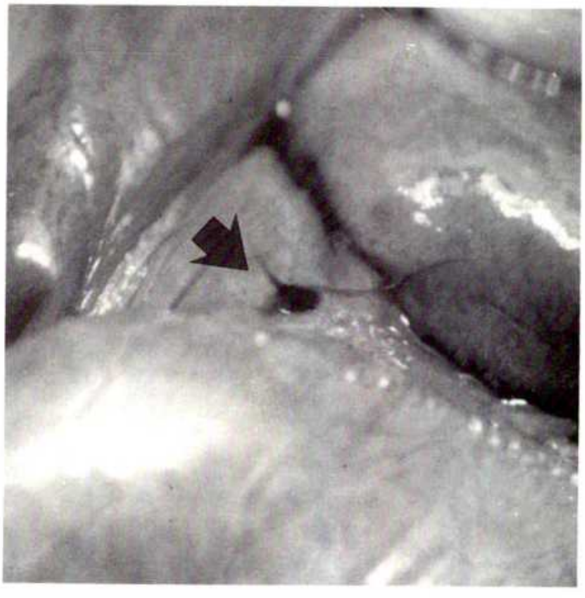

Fig. Hair protruding from pilonidal sinus in coronal sulcus (arrow). Top left shows retracted foreskin and lower half is glans penis.

gery. This is the first patient to present acutely with an abscess which was drained immediately without recurrence. For pilonidal abscess to occur at this site it is postulated that the coronal sulcus acts as a cleft where hair may accumulate and be driven into the shaft and prepuce by the natural movement that occurs between these two surfaces (Fisher *et al.*, 1976). Pilonidal abscess is an unusual cause of penile swelling and has to be distinguished from balanitis and carcinoma. If diagnosed and treated early with sinus excision and circumcision, morbidity from recurrent sepsis can be avoided.

Acknowledgement

We thank Mr J. R. Goldring for permission to present this case.

References

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Goudarzi, H. A. and McColl, I. (1976). Pilonidal sinus of the prepuce. *Br. Med. J.*, **2**, 150.

Requests for reprints to: A. B. Khan, c/o Ward 6, Stobhill General Hospital, Balornock Road, Glasgow G21 3UW.

British Journal of Urology (1992), 69, 439–442

Correspondence

Dear Sir,

re **The dangers of a long urological waiting list.** M. C. Bishop. *Br. J. Urol.*, **65**, 433–440, 1990.

Mr Bishop's reply to correspondence (*Br. J. Urol.*, **68**, 330, 1991) refers to an article of mine as being "typically misleading". I quite understand his pique at my failure to concur in his prejudices, but if he had read our article objectively he would notice that the data base supports the conclusions.

A study with small numbers might be inconclusive in some readers' opinions but it is not flawed. Gentlemen can agree to disagree while still remaining gentlemen.

Yours faithfully,

D. T. Mininberg,
Department of Pediatric Urology, The New York Hospital-Cornell Medical Center, New York, USA.

Dear Sir,

re **Problems in the surgical treatment of interstitial cystitis.** Diane E. Nurse *et al. Br. J. Urol.*, **68**, 153–154, 1991.

The surgical treatment of interstitial cystitis is controversial. The authors of this paper suggest that trigonal biopsy and urethral sensitivity testing may allow better planning of the reconstructive procedure and identify those who will respond to a traditional supratrigonal cystectomy and substitution cystoplasty versus those who may require cystourethrectomy. Certain omissions and assumptions detract from this paper's significance. Firstly, the authors state that all of their patients had histologically proven interstitial cystitis according to generally accepted criteria. To our mind, there are no generally accepted criteria. Attempts have been made to characterise the histological appearance of this disease (M. Holm-Bentzen *et al. J. Urol.*, **137**, 500–502, 1987; J. Gillenwater and A. J. Wein, *J. Urol.*, **140**, 203, 1988) but these are often questioned (P. Hanno *et al. J. Urol.*, **143**, 278–281, 1990). It would be most helpful for the authors to define their histological criteria so that comparison with other series could be made.

The endoscopic appearance, along with pre- and post-operative bladder capacity, frequency and pain, would also be helpful in characterising these patients.

Histological information is also lacking in the 8 patients who had persistent symptoms following subtotal cystectomy. Two patients subsequently underwent trigonal excision, so that tissue should be available from these patients for study.

We do not know what histological criteria the authors used to differentiate a positive trigonal biopsy from a negative one, and detail on urethral sensitivity testing is unavailable. It would also have been of great interest to know whether the patients with initially negative trigonal biopsy, who had persistent symptoms, had repeat biopsies which showed some change.

In terms of the total cystourethrectomy and substitution cystourethroplasty, we learn that one patient has stress incontinence. Are we to infer that all of the others did well, with complete symptomatic relief? Certainly more detailed results are required before we are to contemplate such a sophisticated procedure in these patients.

In the discussion, the authors state that patients with classical Hunner's ulcer achieve tolerably good results from subtotal cystectomy and substitution cystoplasty. They also state that patients undergoing this procedure have a predictable outcome. It is unclear where these statements are derived as the authors' own results reveal a 30% failure rate, and Webster and Maggio (*J. Urol.*, **141**, 287–291, 1989) showed approximately 25% of patients with persistent symptoms following surgery. The major problem for urologists managing painful bladder patients remains the question of who to operate on, and how to predict those who will respond to this surgery. In this respect, the authors have not clarified this problem for us.

Finally, the question of the use of straight versus tubularised segments in this form of reconstruction is of great interest. We would certainly agree that anecdotally, an intact segment with a normally innervated sphincter mechanism allows more predictable voiding, and that potentially patients with a detubularised cystoplasty may require intermittent catheterisation, which may cause persistent urethral hypersensitivity symptoms. Do the authors have cases of detubularised cystoplasties with voiding difficulties to back up their statements? The publication quoted (Nurse *et al. Br. J. Urol.*, **61**, 423–426, 1988) discussed voiding difficulties occurring almost exclusively in neuropathic patients.

In order to find the answer to this complex and frustrating problem, we would make a plea for accurate characterisation of patients, so that results can be compared in as scientific and objective a way as possible.

Yours faithfully,

A. R. Stone, M. B. Roach and J. P. MacDermott
Department of Urology, University of California, Davis, Sacramento, USA.

Dear Sir,

re **Bladder dysfunction due to human T-lymphotrophic virus type I associated myelopathy.** M. Saito *et al. Br. J. Urol.*, **68**, 365–368, 1991.

The authors describe their experience with 4 patients suffering from human T-lymphotrophic virus type I associated myelopathy (HAM). In their report they suggest that the variation between the urodynamic findings in these patients may reflect the extent of CNS involvement. As the clinical course is progressive, initially affecting the thoracic, and later other areas of the spinal cord, producing loss of sacral reflex arcs, they proposed that urodynamic abnormalities would also be progressive, those with initially low residual urinary volumes and detrusor hyper-reflexia progressively building up their residuals and eventually becoming areflexic.

We have recently treated a 73-year-old Jamaican male whose clinical course over 13 years supports this theory. He originally presented in 1973 with poor urinary stream, frequency, urgency and occasional incontinence, which at the time was thought to be due to a urethral stricture. A past history of yaws was noted. He underwent urethrotomy and subsequent repeated dilatations. However, his symptoms failed to resolve and in 1978 he re-presented with similar symptoms, associated now with incontinence, a spastic paraparesis and an unsteady gait. No recurrence of his stricture was demonstrated. Anticholinergics failed to alleviate his symptoms and in both 1979 and 1981 he underwent urodynamic evaluation. On both occasions these revealed a reduced, intermittent free flow rate, a normal resting detrusor pressure, uninhibited detrusor contractions on filling associated with urinary leakage, low volume and normal voiding pressures. Residual urinary volumes were recorded as 70 ml and 0 ml respectively on these occasions.

Over the intervening years between 1981 and 1991 he failed to respond to a range of therapeutic manoeuvres (Helmstein's distension, terodiline, imipramine) and was eventually lost to urological follow-up, his incontinence being managed by an external conveen under the care of his general practitioner and local department of neurology. He developed a progressive myelopathy, initially thought to be secondary to multiple sclerosis rather than any post-treponemal association, but in 1990 was diagnosed by the neurologists as having tropical spastic paraparesis, secondary to HTLV I (synonymous with HAM), on the basis of positive serology and MRI brain scan.

He recently re-presented to us with haematuria. On this occasion, investigations revealed this to be due to an acute infective cystitis, secondary to a high residual urinary volume (>450 ml) proven on ultrasound and subsequent cystoscopy. An IVU did not reveal upper tract embarrassment. He is now being managed by a combination of anticholinergics and intermittent self-catheterisation. He has, however, declined further urodynamic evaluation.

The long interval between initial urodynamic assessment and his recent re-presentation allows some insight into the natural history of this condition. It provides support for the proposition that as HAM progresses, the patient develops impaired emptying and increased residual urinary volumes. A careful appraisal of the report of Saito *et al.* will further support this theory, whereby patient 4 (who experienced the shortest duration of disease) was demonstrated to have a much lower residual urine than patients 1, 2 and 3, who had suffered HAM for longer. This simple observation may be of clinical relevance, such patients periodically requiring ultrasound estimation of their residual urinary volume.

Yours faithfully,

J. McLoughlin,
Department of Urology, Royal Infirmary, Bristol.

Dear Sir,

re **Foley catheter balloon puncture and the risk of free fragment formation.** J. M Chrisp and J. N. Nacey. *Br. J. Urol.*, **66**, 500–502, 1990.

The letter by J. W. D. Ng and A. Y. T. Chan (*Br. J. Urol.*, **68**, 332–333, 1991) about the above paper highlighted their use of the paediatric cystourethroscope to puncture the balloon of a Foley catheter. We have used a flexible cystoscope in a similar way. Using topical local anaesthesia, the flexible cystoscope is passed alongside the catheter until the balloon is visualised. A stylet from a 4F ureteric catheter is used to puncture the balloon after slight traction is applied to the catheter. In order to protect the biopsy channel, a 6F angiographic catheter should be passed and divided flush with the end of the cystoscope before passing the stylet. Any retained fragments can then be retrieved cystoscopically at the same sitting.

Yours faithfully,

M. F. Saxby,
Department of Urology, Wordsley Hospital, Stourbridge.

Dear Sir,

re **Lord's procedure—the best operation for hydrocele?** W. Albrecht *et al. Br. J. Urol.*, **68**, 187–189, 1991.

The authors recommend Lord's procedure as the treatment of choice for all types of hydrocele. They base this statement on their experience in a group of patients aged 16 years or more.

In children, however, virtually all hydroceles are communicating; this means that there is a patent processus vaginalis, which may be very narrow. Moreover, most infants with a scrotal swelling caused by a hydrocele will undergo spontaneous closure of the processus vaginalis with subsequent resolution of the hydrocele. Hence surgical repair is usually reserved for persistent swellings in children aged over 2 years or for a hydrocele that is very large or increasing in size (G. T. Klauber and G. R. Sand (1985). In *Clinical Pediatric Urology*, ed. Kelalis, P. P. *et al.* Philadelphia: Saunders; S. J. Kogan (1987). In *Adult and Pediatric Urology*, ed. Gillenwater, J. Y. *et al.* Chicago: Year Book Medical Publishers).

When repair of a hydrocele in childhood is necessary, it should be performed through a small transverse inguinal incision; this offers a safe approach and allows for diagnosis and ligation of the occult patent processus vaginalis. In children, exploration should never be carried out through a scrotal incision!

Yours faithfully,

R. J. Scholtmeijer,
Department of Paediatric Urology, Sophia Children's Hospital, Rotterdam, The Netherlands.

Reply from Dr Albrecht. In our prospective study we carried out no selection in terms of large, previously punctured or recurrent hydroceles, as in our opinion a comprehensive surgical modality should be applicable to all manifestations of hydrocele. Thus cases of scrotal and spermatic cord hydrocele were included but all patients with congenital hydrocele were excluded.

We fully agree with Professor Scholtmeijer with regard to the congenital open processus vaginalis. In these cases the operative approach should be through an inguinal incision. Of course there are a few boys with a real hydrocele isolated to the scrotum. In all children under 14 years of age a careful history and examination in the supine and upright position should be carried out. In almost all cases it should be possible to find an acquired hydrocele. A careful examination should be made of the inguinal region and scrotum in adults in order to exclude hernias or tumours prior to surgery.

Dear Sir,

re **Comparison of LHRH analogue (Zoladex) with orchiectomy in patients with metastatic prostatic carcinoma.** A. V. Kaisary *et al. Br. J. Urol.*, **67**, 502–508, 1991.

This article concludes that subcutaneous injection of the depot LHRH agonist "Zoladex" is an effective medical alternative to orchiectomy in treating metastatic prostate cancer. Certainly the evidence from this and other studies is very impressive. One of the main problems with the medical treatment is, however, its cost. A single depot injection of the LHRH analogue Zoladex (ICI) is £125.40, this being given every 28 days (according to the manufacturer's guidelines).

In this report Zoladex was given every 28 days and the patients all maintained castrate levels of testosterone during the trial. It would appear that no patients received their injecion even a day late, and so no comment could be made about the longevity of action of a single injection. Reviewing the literature on the administration of depot LHRH agonists (Zoladex in particular), other studies freely alternate the terms 28 days, 4 weeks and monthly when describing their treatment regime. The first two are indeed synonymous but the last is not. This has relevance when considering the cost of treatment in that monthly injections as opposed to 4-weekly would reduce the drug bill by 8% or 1 injection per annum. Certainly the evidence from studies where there has been a delay beyond the allotted 28 days (Emtage *et al. Br. J. Urol.*, **60**, 436–442, 1987) is that castrate levels of testosterone are maintained for at least a further 7 days. In the trial undertaken by Sharifi and Soloway (*J. Urol.*, **143**, 68–71, 1990) they conclude that in most patients a delay of up to 12 days did not result in a clinically significant increase in testosterone.

The conclusion is that the cost of treatment could be reduced by 8% by giving the depot preparation monthly rather than 4-weekly with no adverse effect on the patient and it may even prove possible to increase this to 5 weeks (a saving of 23%). We wait to see whether the advent of the 3-monthly depot preparations will reduce the costs.

Yours faithfully,

C. Bunce
Department of Urology, St Mary's Hospital, London.

Reply from Mr A. V. Kaisary. Throughout the clinical trial programme supporting the use of the LHRH analogue "Zoladex" in the treatment of advanced prostatic carcinoma, therapy has routinely been administered wherever possible at 28-day (4-weekly) intervals.

Emtage *et al.* (*Br. J. Urol.*, **60**, 436–442, 1987) described satisfactory suppression of serum testosterone concentrations provided Zoladex depot injections were administered *within* a 5-week period. Grant *et al.* (*Br. J. Urol.*, **58**, 539–544, 1986) and Turkes *et al.* (*Med. Sci. Res.*, **15**, 477, 1987) reported elevation of serum testosterone concentrations out of the surgically castrate range in increasing proportions of groups of patients in whom the interval for administration of Zoladex was intentionally extended to 5 or 6 weeks. Since the incidence of escape from satisfactory endocrine control in cases of routine monthly or 5-weekly administration compared with 4-weekly administration for either Zoladex or other depot LHRH analogues is unknown from the information currently available, it may be necessary in such cases to consider monitoring serum testosterone concentrations at these extended intervals. This would have implications for both the practical management of patients and the cost of treatment.

Dear Sir,

re **Actinomycotic vesico-uterine fistula from a wishbone pessary contraceptive device.** P. Buckley *et al.* *Br. J. Urol.*, **68**, 206–207, 1991.

The patient described in this case report had incontinence of urine continually for 3 years which appeared to have been due to a vesico-uterine fistula developed from a wishbone pessary contraceptive device. Therefore, I feel the fistula did not arise *because* of actinomycosis, as implied in the title of the article; rather, this was a secondary infection in the pent-up collection of pus in the necrotic cavity above the vaginal stricture.

Yours faithfully,

A. K. Hemal
Department of Urology, All India Institute of Medical Sciences, New Delhi, India.

British Journal of Urology (1992), **69**, 443
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Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth. 21–26 June 1992

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Scholarships for Experimental and Clinical Research in Urology

The European Association of Urology and the European Board of Urology will award three scholarships for research in Urology. Each scholarship will be awarded for one year, starting on 1 July 1992, at a maximum of 33,000 ECU at any appropriate institution in the world. Further information from: The European Board of Urology Education Committee, P.O. Box 25285, 3001 HG Rotterdam, The Netherlands. Tel: 31.10.436.6665. FAX: 31.10.436.6669.

Edinburgh Urological Festival

Edinburgh. 24–27 August 1992

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.

Shackman Travelling Fellowship 1993

Applications are invited from Medical Practitioners registered in the United Kingdom who are either trainees in Urology or Organ Transplantation or Consultant Urological Surgeons or Consultant Surgeons with a major commitment to transplantation of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for application is 1 September 1992.

Further particulars and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB2 9AG.

British Journal of Urology (1992), 69, 444–445

Diary

1992

May 2	International Symposium on Alternative Treatment of Benign Prostatic Hyperplasia. Brussels, Belgium. Contact: Professor C. C. Schulman, Department of Urology, Erasme Hospital, 808 Route de Lennik, B-1070 Brussels, Belgium.
May 6–8	8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.
May 8	Scottish Task Force on Incontinence—Annual Meeting. Southern General Hospital, Glasgow. Contact: Sister Mary Ballentyne, Continence Resource Centre, Southern General Hospital, Glasgow G51 4TF. Tel: 041 425 1117.
May 10–14	American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
May 23–24	Société Belge d'Urologie: 57th Congress. Liège, Belgium. Contact: Dr F. F. Wart, 4 Avenue du Bois des Sartis, B-6111 Landelies, Belgium.
May 24–28	Inaugural Meeting of Pan African Urological Surgeons' Association, Harare, Zimbabwe. Contact: Mr A. P. Danso, Department of Surgery, University of Zimbabwe Medical School, P.O. Box A 178, Avondale, Harare, Zimbabwe.
June 4–5	Second International Workshop and Symposium on New Urological Technology. Leuven, Belgium. Contact: Prof. Dr L. Baert, Department of Urology, Brusselsestraat 69, 3000 Leuven, Belgium. Tel: 016-21 75 32.
June 4–6	Fourth International Meeting of Andrology, Como, Italy. "Treating Male Infertility: New Possibilities". Contact: Dr G. M. Colpi, II Divisione di Chirurgia, Centro di Andrologia e Infertilita, Ospedale "VALDUCE", Via Dante 11, I-22100 Como, Italy.
June 10–12	Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.
June 22–25	Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
June 23–26	BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
July 5–12	ALASKA '92—CRUISE THE INLAND PASSAGE—Breast Imaging at Sea. Contact: ALASKA 92—Breast Imaging at Sea, Medical Seminars International, Inc., 18981 Ventura Blvd, Suite 303, Tarzana, CA 91356, USA.
July 12–19	ALASKA '92—CRUISE THE INLAND PASSAGE—Magnetic Resonance Imaging-Musculoskeletal Imaging at Sea. Contact: ALASKA 92—Magnetic Resonance Imaging at Sea, Medical Seminars International, Inc., 18981 Ventura Blvd., Suite 303, Tarzana, CA 91356, USA.

July 22–25	European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
August 2–5	International Society for Dynamics of the Upper Tract. Ninth Meeting. Akita, Japan. Contact: Dr B. L. R. A. Coolsaet, Klina Hospitals, Campus St Jozefziekenhuis, 2950 Kapellen, Antwerp, Belgium.
August 7–9	Ninth Meeting of International Society for Dynamics of the Upper Urinary Tract. Akita, Japan. Contact: Dr Seigi Tsuchida, Department of Urology, Akita University School of Medicine, 1-1-1 Hondo, Akita, 010 Japan. FAX 81-188-36-2619.
August 24–27	Edinburgh Urological Festival. Edinburgh. Contact: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.
August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
August 24–27	VIIth International Symposium on Urolithiasis and Related Clinical Research. Cairns, Australia. Contact: Dr Rosemary L. Ryall, Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia 5042.
August 30– September 4	Ninth Congress of the International Pediatric Nephrology Association. Pediatric Urology Section. Jerusalem, Israel. Contact: Dr Amicur Farkas, Department of Urology, Shaare Zedek Medical Center, P.O.B. 3235, Jerusalem 91031, Israel.
September 3–6	Tenth World Congress on Endourology and ESWL, Singapore. Contact: Secretariat, c/o Department of Urology, Singapore General Hospital, Outram Road, Singapore 0511.
September 14–18	Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.
September 15–18	Euro-American Conference on Urological Cancer—Clinical and Biological Progress. Athens, Greece. Contact: Erasmus Conference Centre, International Congress Organizers, 227—229 Kifissias Avenue, Athens 145 62, Greece.
September 17–18	Seventh Annual Paediatric Urology Course. Selwyn College, Cambridge. Contact: Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
October 1–2	Continuing Medical Education and Training in Europe: the Future. London. Contact: Dr M. W. N. Nicholls, Conference Office, c/o Fellowship of Postgraduate Medicine, 6 St Andrew's Place, London NW1 4LB. Tel: (44) (0)71 935 5556. Fax: (44) (0)71 224 3219.
October 7–11	1992 Duke Urologic Assembly. "Contemporary Issues in Urology". Pinehurst, North Carolina. Contact: Linda Mace, Assembly Coordinator, Box 3707, Duke Medical Center, Durham, NC 27710, USA.
October 9–10	BAUS Autumn Meeting, Swansea. Contact BAUS Office.

British Journal of Urology (1992), 69, 446–448

Book Reviews

Manual of Urology. Diagnosis and Therapy. Edited by M. B. Siroky and R. J. Krane. Pp. xiii+313. Boston, London, Toronto: Little, Brown and Company. 1990. Price: £9.95.

This spiral-bound manual apparently represents a distillation of the instruction given to residents in the Boston University Training Program. It contains a vast amount of factual material, mainly in list form, described didactically and as such must be regarded as an aid to preparation for examinations, and perhaps the FRCS Urol! It does not aim to stimulate interest for controversial discussion. Even with its limited objectives, much of the verbiage could have been replaced by diagrams. The few photographs provided are of insufficient quality to distinguish key features, as for example between different sorts of catheters and sounds. The drawback in the organisation of the book seems to be a failure to decide whether the starting point for discussion should be clinical presentation or specific diseases. Algorithms are always a problem and this treatment may not always be appropriate, particularly if it cannot be comprehensive. In Chapter 1 the distinction between acute and chronic obstruction is not clarified, nor are the actual abnormal radiological findings described The selection of "retroperitoneal fluid collections" is odd as it is hardly an entity in its own right. Nowhere is the investigation of the "non-functioning kidney" considered.

The overall impression is of a rather outdated text. The use of ultrasound in diagnosis is not emphasised. The recommendation of cystoscopy to assess prostatic enlargement is surely irrelevant these days and if there is any doubt on a clinical diagnosis of outflow obstruction even supported by ultrasound assessment of residual urine and peak flow measurements, videocystometry is surely required.

The chapter on urological emergencies is redundant as so much has been left for discussion elsewhere. Even so, a differential diagnosis and management of renal pain would have been helpful. There are a few important factual omissions. Surely mannitol rather than loop diuretics is the treatment of fluid overload in the TURP syndrome and calcitonin and diphosphonates should feature in the treatment of acute hypercalcaemia.

Despite these drawbacks this book does fill the gap as an inexpensive factual crammer, although it is unlikely to provide enough practical information to prevent a urological trainee seeking more senior help.

Paediatric Nephrourology: Progress in Research and Practice. Edited by H. Hoey and P. Puri. Pp. xi+96. Chichester, New York, Brisbane, Toronto, Singapore: Wiley. 1990. Price: £16.95.

This is a delightful little book that records the papers given at a Symposium on Recent Advances in Paediatric Nephrourology to mark the retirement of Dr Raymond Rees from The National Children's Hospital, Dublin. Within its 96 pages there are some gems of chapters based mostly on urinary tract infection in children with its complications of kidney scarring and hypertension. Jean Smellie and Tony Risdon provide a more succinct update on reflux nephropathy than could be found anywhere at present. Prem Puri gives a convincing description of the endoscopic injection technique to stop reflux. A longer contribution by Hilary Hoey discusses the diagnosis and management of the child with intersex in an understandable manner despite a few unfortunate spelling errors. Other chapters include the treatment of idiopathic nephrotic syndrome and renal hypertension and the imaging and bacteriology of children with urinary infection. The idea of this book has worked well.

Radionuclides in Nephro-urology. (Contributions to Nephrology, Volume 79). Edited by M. D. Blaufox, N. K. Hollenberg and C. Raynaud. Pp. xi+232. Basel: Karger. 1990. Price: SFr. 193.–; DM 231.–; £80.50; US$ 128.75.

This is the proceedings of a symposium of the same name held in Williamsburg, Virginia, in May 1989. The proceedings of previous symposia in the same series have appeared under the same title. There is no indication that this is one of a series and the title could therefore be a little misleading.

The volume itself consists of an invited review followed by papers grouped under 6 headings—radiopharmaceuticals, renal function, renal imaging, paediatrics, hypertension and special reports of collaborative studies. The invited paper by Hollenberg and Williams is a review of angiotensin and ACE inhibition. The other papers all consist of extended abstracts of about 1500 words of the papers presented at the meeting. Most of the papers include a few figures and references. The book is well produced on good quality paper and the reproductions are in general of a very high standard.

Most, if not all, of the topics are covered at greater length and more detail in papers which have by now been published in readily available journals. This publication will have, therefore, very limited appeal.

The Cryptorchid Testis. Edited by T. O. Abney and B. A. Keel. Pp. 176. Boca Raton, Florida: CRC Press, Inc. 1989. Price: £84.00.

This book reviews largely experimental data relating to the effects of cryptorchidism on individual testicular cell types and inter-cell relationships. The text is well illustrated with black and white line drawings, photomicrographs and histograms and is supported by extensive bibliographies. It is not, however, as the preface suggests, "a current comprehensive review of cryptorchidism".

For example, factors involved in maldescent are given scant attention, with reference to current concepts scattered throughout various chapters. Also, there is marked variation in quality between chapters. The chapters on experimental models and steroidogenesis are particularly good. The presentation of concepts relating to the retractile testis, classification of undescended testes, and the mechanism of normal descent are outdated. The discussion of fertility and cryptorchidism is thorough but destroyed by the final paragraph referring to "the significant degree of hypo fertility . . . in unilateral cryptorchidism"—a statement unsupported by the available facts. The book deals primarily with animal experimental research and its niche lies either in a specialised laboratory or large university medical library.

Structure and Function of the Kidney (Comparative Physiology, Volume 1). Edited by R. K. H. Kinne. Pp. viii+200. Basel, München, Paris, London, New York, New Delhi, Bangkok, Singapore, Tokyo, Sydney: Karger. 1989. Price: £68.80.

This is the first volume of a series dedicated to comparative physiology. Perhaps the title could have indicated more clearly that the book deals almost exclusively with fish and reptile kidneys. As such, it is likely to be of limited appeal to clinicians. This said, it is a comprehensive review by authors who have obviously contributed extensively to this area of knowledge. There are frequent points of interest: for example, the fact that all species other than mammals and agnathan fish have a renal portal venous system; the huge, multi-tubular glomerulus or "glomus" of the lamprey; the relationship between the primitive process of tubular secretion which substitutes for glomerular filtration in aglomerular fish, and proximal tubular ion and organic acid secretion in mammalian kidneys; and the hypothesis that cilia on the luminal border of proximal tubules in marine teleosts serve to prevent stone formation in the presence of low urine flow. There is a detailed physiological study of the hagfish kidney, which functions as an "on-off" fluid release valve, without tubular sodium chloride reabsorption. A chapter is dedicated to the concept that proximal tubular secretion of sodium chloride, seen in aglomerular fish, also occurs in glomerular fish and mammals. The final chapter is an extremely detailed review of current knowledge of the nephron in reptiles. Unfortunately, many sections begin with the phrase "almost nothing is known", although the author refers to 44 of his own publications.

Overall, the book would benefit from a more correlative approach to make it of more general interest. There is a shortage of conclusions, particularly regarding implications for mammalian physiology and pathology, and the reader is often left to judge the significance of the findings for himself. It will, however, be a valuable reference volume for those working in the field, and for those seeking a wider perspective on the complexities of kidney function.

Growth and Endocrine Changes in Children and Adolescents with Chronic Renal Failure. (Paediatric and Adolescent Endocrinology, Volume 20). Edited by K. Schärer. Pp. viii+188. Basel, Munich, Paris, London, New York, New Delhi, Singapore, Tokyo, Sydney: Karger. 1989. Price: £74.20; US$ 118.75; DM 213,–.

A degree of consensus and stability has now been achieved regarding management of chronic and end-stage renal failure in infants and young children. The opportunity thus available for reflection on outcome shows the most pressing current problem to be that of poor growth despite attempts to maximise caloric intake and to achieve normality in terms of body homeostasis. Indeed the demonstration that supraphysiological doses of recombinant human growth hormone (rhGH) are capable of achieving substantial increments in linear growth is about to open a difficult cost/benefit debate (at £5–£10,000 per child per year).

This volume is a useful amalgam of both review and some original data derived from experts in growth and development, paediatric endocrinology and paediatric nephrology.

There are excellent reviews on the methodology of growth assessment by M. A. Preece, the physiology of growth hormone in health and renal disease by D. R. Powell *et al.*, vitamin D metabolism in uraemia by R. W. Chesney and changes in the hypothalamic-pituitary axis in uraemic children by F. Perfumo and R. Gusmano.

Other chapters review the difficulties in achieving improved linear growth with conservative management in chronic renal failure, early promising (and now overtaken) studies on the use of rhGH and on the paradoxically beneficial results of transplantation on sexual maturation yet with its disappointing results in terms of linear growth.

The remaining chapters are of general endocrinological interest but basically make-weight for this typically expensive Karger production which includes 68 figures and 20 tables along with many useful references for the field.

The volume provides mutually useful reading for both paediatric nephrologists and endocrinologists, all of whom should have access to a copy, but will have a limited priority for urologists and surgeons.

Clinical Management of Renal Cell Cancer. Edited by J. E. Montie, J. E. Pontes and R. M. Bukowski. Pp. xiii+185. Chicago, London, Boca Raton, Littleton: Year Book Medical Publishers. 1990. Price: £42.50.

The authors challenge the commonly held belief (by many urologists) that there has been no significant change in the management of renal cancer in the past decade, or even 2 decades. However, these authors claim "remarkable changes in the diagnosis and treatment of RCC". On the question of diagnosis, if that means earlier diagnosis and better staging, then there is good agreement. There is now good evidence that the more widespread use of ultrasound will produce more "incidental" renal cancers—whose removal will improve the overall results of any series. If diagnosis also means staging, then imaging techniques have helped to define better the extent of the tumour. This book is well illustrated on these aspects.

Treatment options are well described—radical nephrectomy, lymphadenectomy, an out-of-date commentary on angio-infarction, inferior vena cava thrombectomy and biological response modifers. True progress is not always easy to measure but this is a worthy (though expensive) attempt to give a full picture of current attitudes.

Renal Tract Stone. Metabolic Basis and Clinical Practice. Edited by J. E. A. Wickham and A. C. Buck. Pp. xiii+662. Edinburgh, London, Melbourne, New York: Churchill Livingston. 1990. Price: £75.00.

This present decade has seen a revolution in the management of stones in the urinary tract. So much has been spoken and so much written on the technological advances that other aspects of stone disease may appear to be of relatively little importance. The distinguished urological editors point out that despite these startling surgical developments, physicians, biochemists, physiologists and research workers in other disciplines have not been idle in their quest for an understanding of the biochemical and metabolic abnormalities associated with stone formation.

The purpose of this book was therefore to bring together a galaxy of international experts in *res lapidea* There are more than 60 contributors and approximately two-thirds of the book cover the metabolic basis of stone disease. A recurring question by urologists is who to screen and in what detail should screening be pursued to find a metabolic cause for stones; this debate is well handled in respect of idiopathic urolothiasis but a chapter devoted to pathways or algorithms, albeit dogmatic, would have been a useful addition.

As might be expected, the sections on open surgery, percutaneous surgery, ESWL and ureteroscopy are first class descriptions of these procedures.

This book truly deserves its place as the standard text on renal tract stones and will be an essential book in urological departments and medical libraries.

Common Problems in Infertility and Impotence. (Common Problems in Urology Series). Edited by J. Rajfer. Pp. xvii+390. Chicago, London, Boca Raton, Littleton: Year Book Medical Publishers. 1990.

The scope of the book covers infertility and impotence. Each section is introduced by an example clinical problem and this helps to unify the style and will allow the clinician quickly to find the section relevant to any current problem. The disadvantage of this format is that it makes it more difficult to read about a subject and thus less useful for urological trainees. The various sections are written by 56 contributors who are, with one exception, from North America. With so many contributors there is bound to be some repetition but many of the sections are excellent.

The book should be useful to practising clinicians as it documents well current North American clinical practice.

Megaureters in Children. By J. Dvoracek. Pp. 215. Acta Universitatis Carolinae. Medica. Monograph CXXXVI. 1990. Prague. Price: 30 Kcs.

Megaureter is a difficult topic because it encompasses a wide variety of conditions. There have been numerous attempts to establish an acceptable international classification. This new text will be welcomed by paediatric urologists.

The first 6 chapters are devoted to a review of the anatomy, physiology, pathology, classification and current management. This is a comprehensive review of 100 pages. There is perhaps insufficient mention of recent developments in our understanding of the pathophysiology of ureteric obstruction. Also, the emphasis on definitive surgery for megaureter based on radiological anatomy does not fit our current concept that dilatation does not equate with obstruction and "obstruction" may therefore not need surgery Similarly, many would opt for a more conservative approach to ureteric reflux than that advocated by Dr Dvoracek. The merits of extensive surgical remodelling are very debatable. The next 3 chapters are a retrospective review of the author's experience with 150 patients. This comprehensive review gives excellent material for internal analysis and is easy to compare with other studies. The diagrams and print are of good quality and the text has not suffered at all by translation into English.

The author has provided an excellent work of reference for anyone interested in megaureter. He should be congratulated on producing a beautiful book under extraordinarily difficult circumstances.

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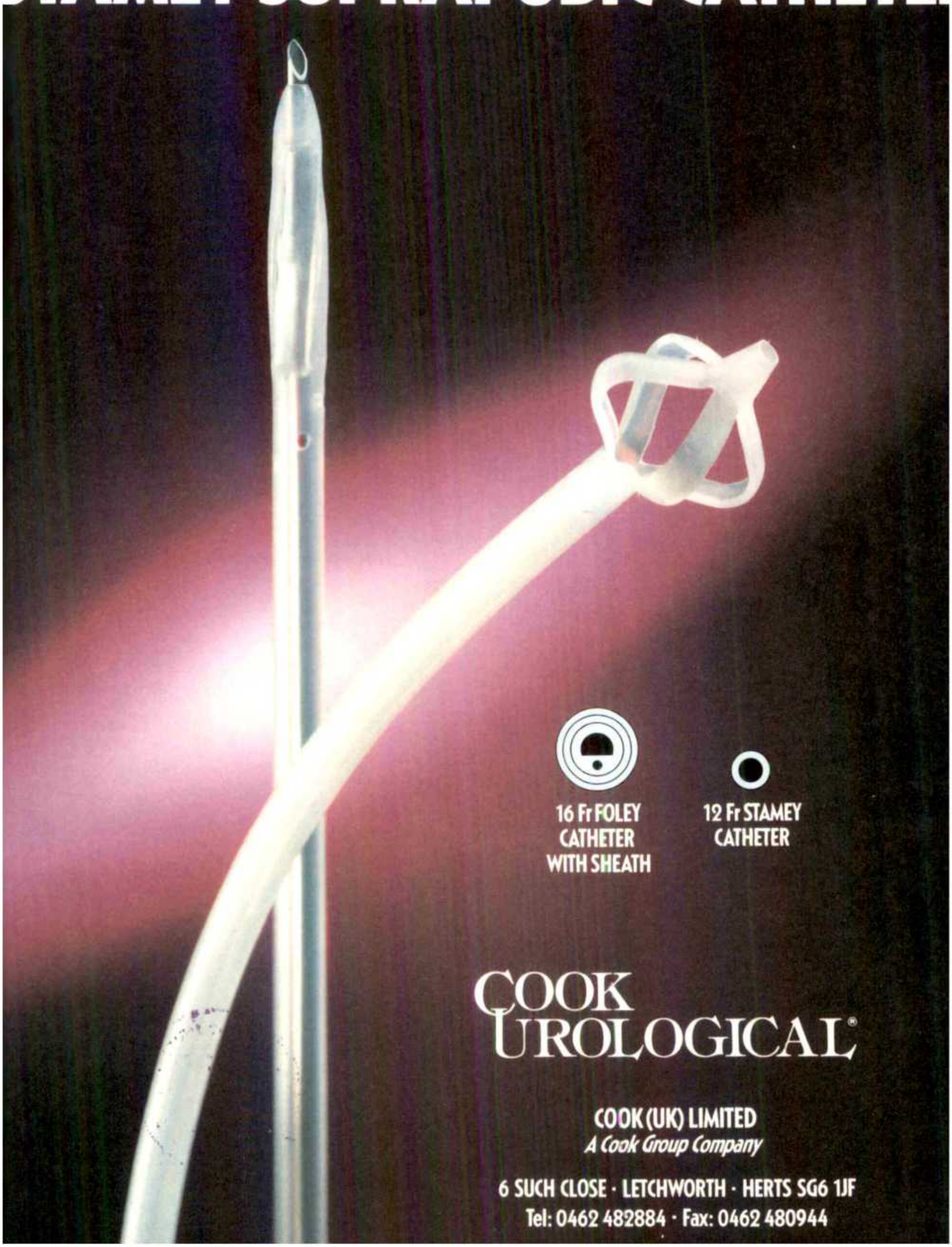

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REVIEW

Transrectal Ultrasound 1992

D. RICKARDS

Department of Radiology, Middlesex Hospital, London

Transrectal ultrasound (TRUS), computed tomography (CT) and magnetic resonance imaging (MRI) directly image the prostate and have been extensively investigated. TRUS has rapidly progressed since its clinical introduction (Watanabe *et al.*, 1971) and now has its advocates, enthusiasts, doubters and adversaries. There are understandable reasons irrespective of what position is adopted. There has been confusion about what cancers look like and whether TRUS can accurately detect and stage malignancy. Probe technology rapidly advances, providing more detailed anatomical information. Colour Doppler and 3-dimensional reconstruction are now possible. Functional as well as anatomical parameters can be measured. The anatomy of the gland has been redefined. These advances compound the difficulties in understanding the place of TRUS in urological diagnosis. What is learned and practised one year is out of date the next—not good for credibility.

Technique and Biopsy Methods

Transverse axial sections of the prostate (like CT images) provide anatomical detail of the gland symmetry, the seminal vesicles and zonal anatomy. Sagittal sections are essential for imaging the urethra and its surrounding tissues and the configuration of the prostate in relation to the bladder base. Multiplane imaging is essential and this can be achieved with a variety of probes. Biplane probes allow for transverse axial and sagittal imaging using 2 transducers housed at the end of the same probe. The resolution afforded by each transducer is currently limited by probe diameter and whilst good spatial resolution is achieved with 7MHz linear array transducers providing sagittal sections, the transverse axial images are less good and in general use 5 MHz transducers. Guided biopsy is generally by the perineal route.

Transrectal guided biopsy ideally requires a multiplane "end-viewing" transducer in which the scan planes are centred along the long axis of the transducer and are altered by rotating the housing of the probe. Any suspicious area can be readily scanned in 3 dimensions. Most commercially available ultrasound (US) machines provide adequate anatomical definition of the prostate, but cheaper units bought and used by urologists in their own departments will become relatively less useful as the expensive technology of pulsed and colour Doppler makes an impact in prostate imaging.

With advancing probe technology, transrectal as opposed to perineal biopsy is the most accurate method. All areas of the gland can be biopsied. Local anaesthesia is not necessary and it is done on an out-patient basis. It is almost painless provided the anal sphincter is avoided. There are no significant complications, but prophylactic antibiotics should be given immediately before and for 2 days after the procedure (Torp-Pederson and Lee, 1989). The risk of faecal contamination is reduced by using a cleansing enema before biopsy. If biopsy of a palpable lesion is negative for malignancy, digitally-guided biopsy should be undertaken because not all palpable lesions are seen on TRUS. Perineal biopsy is a safe and a perfectly acceptable option for biopsy and does not necessitate prophylactic antibiotics. It does require the extensive use of local anaesthesia to the skin, subcutaneous tissues and pericapsular area, typically 15 ml of 1% lignocaine. It is preferable if prostate abscess or inflammatory disease is suspected. A 2-cm core

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biopsy using an automatic triggering device and 18 gauge needle has replaced aspiration cytology. The needle tip must be placed well proximal to a suspicious lesion.

Ultrasound guided biopsy is more accurate than digitally guided procedures even when malignancies are palpable; 35 to 39% of palpable tumours missed by digitally directed biopsy are subsequently confirmed by ultrasound guidance (Rifkin *et al.*, 1991).

Prostate Anatomy

Lowsley's description of the prostate as a gland of 5 lobes (Lowsley, 1912) has been superseded by McNeal's concept of zonal anatomy (McNeal, 1968; Blacklock and Boushill, 1977). Three glandular zones (peripheral, central and transitional) and one non-glandular zone (fibromuscular stroma) can be identified on TRUS and MRI. Normally the transitional zone, which accounts for 5% of prostate volume, is located around the proximal posterior urethra and its ducts run parallel to the urethra to emerge proximal to the distal sphincter mechanism. Calcification within these ducts forms the boundary at endoscopic resection, the surgical capsule. It is within this zone that hyperplasia and 10% of cancers develop. The central zone accounts for 25% of normal glandular tissue, is cone-shaped and narrows at its apex near the verumontanum. Where the ducts of the vas deferens and seminal vesicles join to form the ejaculatory ducts, which then pass through the central zone, there is an absence of capsule through which tumours can readily extend (Lee *et al.*, 1989); 5 to 10% of cancers originate in the central zone. The peripheral zone constitutes 70% of normal glandular tissue. It envelops the other zones to form the postero-lateral and apical parts of the prostate and is the site of origin of 70% of cancers. At its apex, the prostate capsule is thin or absent and the obliteration of a trapezoid area formed by the peripheral zone proximally, rectourethralis muscle distally and membranous urethra anteriorly indicates extension of tumour beyond the peripheral zone (Lee *et al.*, 1989). The anterior portion of the prostate is the non-glandular fibromuscular stroma.

The transitional and central zones are both hypoechoic, heterogeneous and cannot be separated by their tissue characteristics alone, a knowledge of their respective anatomical locations being more important. The peripheral zone is homogeneous and echogenic. In addition, the vas deferens, seminal vesicles, distal ureters and bladder base are well seen. Like TRUS, MRI can delineate zonal anatomy with T2 predominant images using the urethra as a key landmark.

Prostate Cancer

Prostate cancer has received much attention recently because of improved detection using TRUS, understanding its biological behaviour more clearly, and advances in surgical techniques (Walsh *et al.*, 1988). The diagnosis of malignancy on digital examination depends upon its size, location and consistency; findings are subjective. TRUS can detect non-palpable malignancies (Lee *et al.*, 1991) but is also subjective, considerable experience being needed to interpret the images correctly. TRUS cannot detect microscopic spread of malignancy either within the gland or into the prostate capsule, nor can it detect tumours that are isoechoic with surrounding normal prostatic tissue on images alone, but colour Doppler assisted US can. Malignant potential correlates with tumour volume, histological grade and stage. Tumour size is important in determining the natural history of prostate cancer and can be used to predict capsular infiltration, differentiation and metastatic spread (McNeal *et al.*, 1986).

At the beginning of the 1980s, cancer was described as echogenic, often indistinguishable from calcification (Brooman *et al.*, 1981). At the end of the decade, cancer is predominantly echopoor (Fig. 1). Isoechoic cancers are common and mixed echogenic and hyperechoic tumours are described. Current TRUS technology permits a spatial resolution of 0.2 mm. Sharply focused probes permit excellent near-field definition. Small peripheral malignancies are identified and proven by TRUS guided biopsy. Large series have shown good pathological correlation with TRUS images (Griffiths *et al.*, 1987) and the confusion about what tumours look like has been largely resolved.

Only 20% of peripherally situated hypoechoic lesions are malignant (Rifkin and Choi, 1988). There is no single pathognomic appearance of prostate cancer by TRUS criteria. It is clear that smaller malignancies are more hypoechoic than larger ones and that the majority of large tumours are not hypoechoic. Tumours have an irregular outline and capsular distortion is suggestive of invasion. Not all carcinomas can be detected by TRUS. Up to 25% are isoechoic, with normal prostate tissue (Salo *et al.*, 1987). In a study of 125 radical prostatectomy specimens in patients with proven T0 and T1 tumours, 76% were prospectively

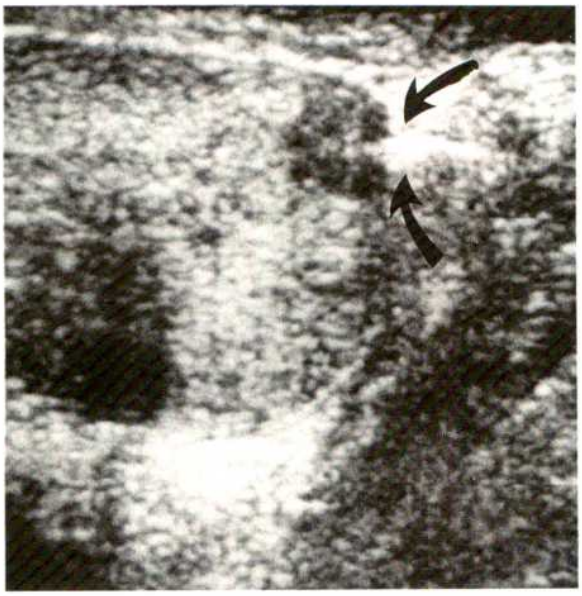

Fig. 1 Sagittal TRUS. A small, hypoechoic and peripherally located lesion suggestive of malignancy which can only be proven by biopsy (arrow on needle tip).

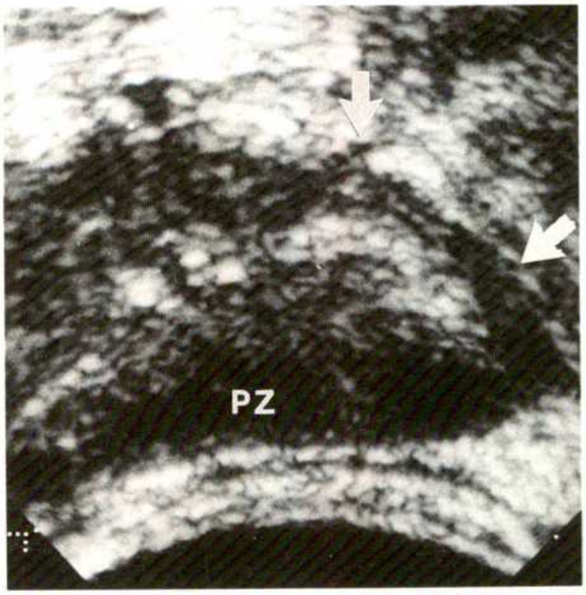

Fig. 2 Transverse axial scan of T3 prostate cancer. The peripheral zone (PZ) is predominantly echopoor. Capsular echoes are indistinct and there are defects in it (arrows).

identified on TRUS because of their hypoechoic nature and 24% missed because they were isoechoic (Hamper *et al.*, 1991). Apparent echogenic malignancies are due to those involving the corpora amylacea and in some high grade tumours due to comedonecrosis, centrally necrotic tumours with calcification that appears fine and stippled on TRUS (Hamper *et al.*, 1990).

A crucial factor in staging prostate cancer is determining whether the tumour is confined to the gland and potentially amenable to radical prostatectomy (Walsh and Jewett, 1980). CT, MRI and TRUS are advocated as staging modalities in patients with clinically localised tumour. CT cannot detect intracapsular malignancy and has no role to play (Rickards *et al.*, 1983). On TRUS, localised deformity of the capsule or an interruption in the normally bright capsular echoes (formed by the interface of prostate with periprostatic fat and probably not the true capsule of the prostate) suggests involvement (Fig. 2). When these criteria are applied to the peripheral zone, 68% of tumours that can be detected by TRUS are correctly staged (Hamper *et al.*, 1991). There is considerable overlap in the appearance of benign and malignant disease in the rest of the gland. TRUS does not provide such good definition of the anterior capsule of the gland, especially when there is prostatomegaly. Thus staging is only potentially possible in the 75% of hypoechoic tumours that arise in the peripheral zone (70% of tumours).

Lesions that look like cancer

A large proportion (80%) of peripherally located echopoor lesions are not due to adenocarcinoma, but to nodules of benign hypertrophy, cysts, infarcts, inflammatory processes, cystic atrophy, blood vessels, muscular tissue and malakoplakia (Chantelois *et al.*, 1990). Recent work in this department suggests that colour Doppler may help in further defining which echopoor lesions are malignant. In a preliminary study, malignant lesions were seen to be vascular except in patients with recurrent disease previously treated by radiotherapy. There has been a clear separation between benign and malignant processes, but we cannot yet state that an echopoor peripheral lesion in which no appreciable blood flow can be seen is benign. With generally available technology, the positive predictive value (the percentage of abnormal lesions on TRUS that are malignant) is about 25%.

Post-radiotherapy monitoring

Following radiotherapy for localised cancer, the prostate becomes small and echogenic. Persistent or recurrent tumour is difficult to detect, but TRUS is emerging as an effective modality in some cases. Persistent tumour maintains its pre-treatment echo characteristics, mainly an echopoor lesion, and lesions over 5 mm in diameter persisting for 12 months following radiotherapy are specifically suspicious of malignancy and should be biopsied (Egawa *et al.*, 1989). A decrease in total prostate volume is not a reliable indicator of prognosis (Clements *et al.*, 1989). This is not surprising, since coexistent normal and hypertrophied prostatic tissue will shrink in response to radiotherapy. Measuring prostate specific antigen (PSA) is probably more useful in the follow-up of prostate cancer (Shearer, 1991).

Should TRUS be used for Screening?

Despite improvements in treatment and detection, the mortality rate from prostatic carcinoma has not declined over the past 3 decades. The purpose of screening would be to detect clinically significant disease at a low cost without creating emotional trauma. Any screening test must have a high sensitivity (be able to detect malignancy, preferably 100%) and a high specificity (be able to confirm that no malignancy exists) and not place too heavy a burden on the country's health care system. The costs of screening are very high. Chodak and Schoenberg (1989) reported that assuming screening takes 15 min to perform at a conservative cost of $150 per TRUS and $450 per biopsy, 5000 physicians would have to work a 40-h week for 35 weeks each year to screen all men over 50 years of age in the USA at a total annual cost of $7 billion. They further pointed out that if 30% of 25 million men older than 50 years had cancer detected by screening and subsequently treated by radical prostatectomy, a 1% mortality rate would produce 75,000 deaths, 45,000 more than would be expected to perish due to the carcinoma itself. There is debate concerning the natural history of incidentally found cancer and whether it is worth screening. A series of 223 patients with localised cancer and no evidence of metastases were left untreated (Johansson *et al.*, 1989). In a 3- to 10-year follow-up, 16 of 83 deaths were considered due to prostate malignancy. Tumour grade at the time of diagnosis was the important prognostic factor. Of 148 patients with well differentiated tumours, progression occurred in 19% and death in 2.5%. In 9 patients with poorly differentiated tumours, progression occurred in 67% and caused death in 56%. They concluded that early stage prostate cancer has a low mortality rate.

The measurement of prostate specific antigen, digital rectal examination and TRUS are in current screening use. Measurement of prostate volume by computed planimetric methods (Jones *et al.*, 1989) alters the interpretation of PSA levels. They are raised approximately 0.3 ng/ml per gram of tissue in benign hyperplasia compared with 3.5 ng/ml per gram of tissue in cancer (Stamey and Kabalin, 1989).

In a screening study of 784 self-referred men, Lee *et al.* (1988) reported an improved detection rate for TRUS over digital examination (2.6% *vs* 1.3%), but other reports showed no such difference (Palken *et al.*, 1991). In practice, a normal TRUS in men over 50 is rarely seen. There is likely to be some enlargement due to benign prostatic hyperplasia (BPH); calcific foci in the corpora amylacea and elsewhere in the gland are very common. TRUS is not good at detecting the 30% of tumours that arise in the central and transitional zones and only the minority of peripherally located hypoechoic lesions represent cancer (Rifkin and Choi, 1988). There is sufficient evidence to suggest that TRUS improves the early diagnosis of prostate cancer, but not at the expense of a good rectal examination.

Benign Prostatic Hyperplasia

BPH originates in the transitional zone and increases the anteroposterior dimension of the prostate, which assumes a more spherical configuration. The central and peripheral zones are compressed. BPH associated with bladder neck dyssynergia causes minimal enlargement of gland dimensions (the trapped prostate) (Turner Warwick *et al.*, 1973). The echogenicity of discrete adenomas varies greatly, making coexistent malignant disease very difficult to identify. In practice, clinical suspicion of malignancy, biochemical confirmation and a TRUS which does not suggest tumour in any part of the gland requires multiple biopsies, including the apparently benign adenoma. BPH can be associated with cystic degeneration and dystrophic calcification.

Prostatitis and Prostate Abscess

The appearance of prostate abscesses is characteristic on TRUS. They can be drained under TRUS control via the perineal route to avoid further contamination. Their response to treatment can be monitored.

Prostatic inflammatory disease has no characteristic appearance. Echogenic and echopoor foci throughout the gland have been reported (Doble *et al.*, 1989) as well as prominence of the periprostatic venous plexus (Griffiths *et al.*, 1984) and small calcific foci seen in the periurethral area. Colour Doppler suggests a generalised increase in blood flow throughout the gland, but specifically in the periurethral region. Intraprostatic reflux has been invoked as a cause (Kirby *et al.*, 1982).

Observations in this department in some patients with symptomatic prostatic inflammatory disease in whom small punctate calcific opacities are identified on both plain film radiology and TRUS, usually asymmetrical and located in the transitional zone, have subsequently revealed urodynamic evidence of bladder neck dyssynergia. In addition, TRUS has shown there to be a prominent echopoor mass enveloping the posterior urethra, but predominantly anterior to it; this incorporates the bladder neck mechanism which on biopsy has been shown to be smooth muscle with no prostatic acini. Such TRUS findings seem characteristic of bladder neck dyssynergia, as similar appearances have not been seen in normal patients or in those with outflow obstruction due to other causes.

Seminal Vesicle Imaging and Infertility

Congenital cysts of the seminal vesicles are uncommon and associated with other genitourinary anomalies (Kenney and Leeson, 1983), such as ectopic insertion of the ipsilateral ureter, ipsilateral renal dysgenesis (80%) and duplication of the ureter (8%). They present in patients aged to 20 to 40 years with pelvic or perineal pain exacerbated by ejaculation. Removal or drainage of the cysts always results in relief of symptoms. Drainage under TRUS guidance is easily done. Cystic dilatation of the seminal vesicles can occur following TURP as a result of scarring and obstruction to the ejaculatory ducts. Prostate tumour can also obstruct the ejaculatory ducts. If there is doubt as to whether the dilated seminal vesicle is responsible for the patient's symptoms, TRUS before and after ejaculation will help. If not obstructed, the seminal vesicle will decompress. Primary seminal vesicle malignancies are rare, but secondary involvement from primary prostatic, bladder or rectal carcinoma is more common. Such involvement distorts the seminal vesicle and lesions will be identified in continuity with the primary tumour. An echopoor rim to the ejaculatory duct or obliteration of it by tumour also suggests seminal vesicle involvement (Lee *et al.*, 1989). Prostate tumours over 2 cm in diameter usually involve the seminal vesicle (Scardino *et al.*, 1989). Such findings suggest T4 disease.

Although haemospermia is usually associated with seminal vesicle and ejaculatory duct calculi (Fig. 3), it has been reported in unexpected prostatic and seminal vesicle malignancy. It is a condition which alarms patients considerably. As a preliminary investigation, TRUS can usually find a cause and can usually exclude a sinister aetiology.

TRUS is useful in the investigation of infertility should an obstructive lesion be suspected. Müllerian duct remnants, vas deferens and ejaculatory ducts can be clearly seen.

Other Urological Uses of TRUS

The balloon of a Foley catheter that defies deflation by non-invasive means can be punctured under TRUS control *via* the perineal route very easily, with considerably less pain and more accuracy afforded by the suprapubic-transabdominal approach (Walters *et al.*, 1988). Permantly implanted prostate stents can be placed under TRUS control (Milroy *et al.*, 1989; Chapple *et al.*, 1990), although placement under direct vision is more accurate. Pre-operative measurement of prostate length, from bladder neck to verumontanum, is useful for deciding on which length of stent to deploy. The post-operative position and dimensions of the stent, its relationship to the sphincter mechanisms and the degree of urothelial lining can be monitored by TRUS (Fig. 4). Prostatic thermotherapy catheters are of varying lengths and accurate measurement

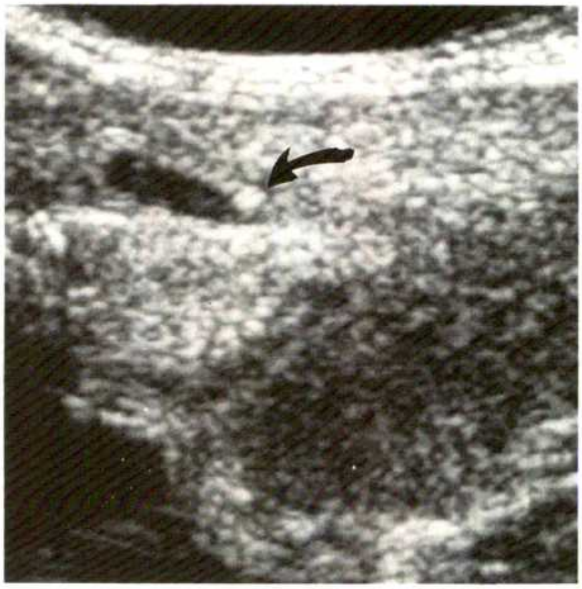

Fig. 3 Sagittal TRUS of a dilated ejaculatory duct due to a small stone (arrow).

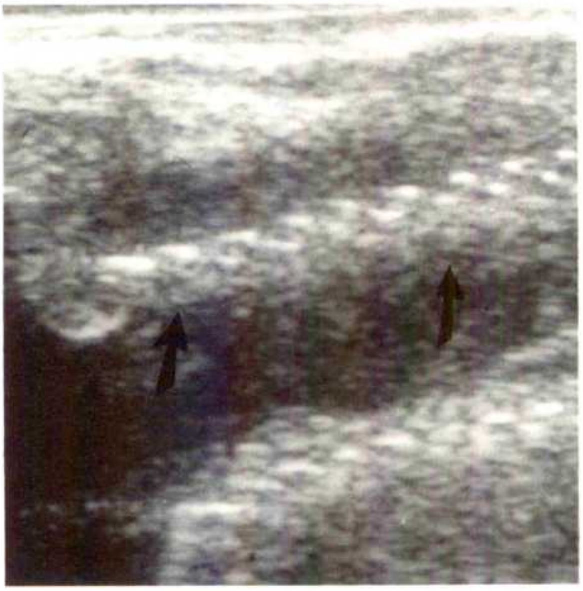

Fig. 4 Sagittal TRUS 6 months following insertion of a Wallstent endoprosthesis. The stent is in excellent position at the bladder neck and there is demonstrable urothelial covering (arrows).

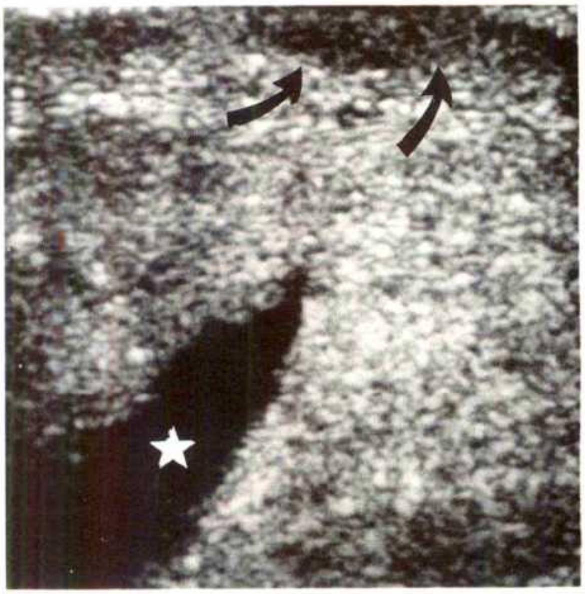

Fig. 5 Sagittal scan showing a good TUR cavity (*) in a patient with echopoor lesions in the peripheral zone due to biopsy proven cancer (arrow).

of prostate length by TRUS is needed to decide which catheter to use.

TRUS should ideally be performed on all adult males undergoing urodynamic assessment. Videocystometry provides anatomical detail of the internal anatomy of the urethra and the likely point of obstruction to the outflow tract. It seems logical to look at the structures surrounding the urethra and TRUS adds very little time to the whole procedure. It is particularly useful in assessing TURP cavities (Fig. 5) in patients who remain symptomatic and defining the cause of outflow obstruction in a patient with a digitally normal sized gland in whom the TRUS findings of bladder neck obstruction may be identified. A wide open bladder neck can be identified in patients with detrusor sphincter dyssynergia (Shabsigh *et al*., 1988) and those who have congenitally incompetent bladder necks (Fig. 6) who present with retrograde ejaculation. TRUS is also contributory in assessing bladder to urethral relationships in females with urinary incontinence and urodynamic parameters are not affected (Richmond and Sutherst, 1989).

In conclusion, prostate tumours are predominantly hypoechoic on TRUS. TRUS can detect non-palpable malignant tumours, but the diagnosis can only be confirmed by biopsy. TRUS guided biopsy is more accurate than digital guidance. Transrectal guided biopsy is preferred to the perineal route. Screening for prostate cancer with TRUS is expensive, requires considerable manpower and is not yet feasible. TRUS is of little value in the follow-up of treated prostate cancer but is useful as an adjunct to lower tract urodyn-

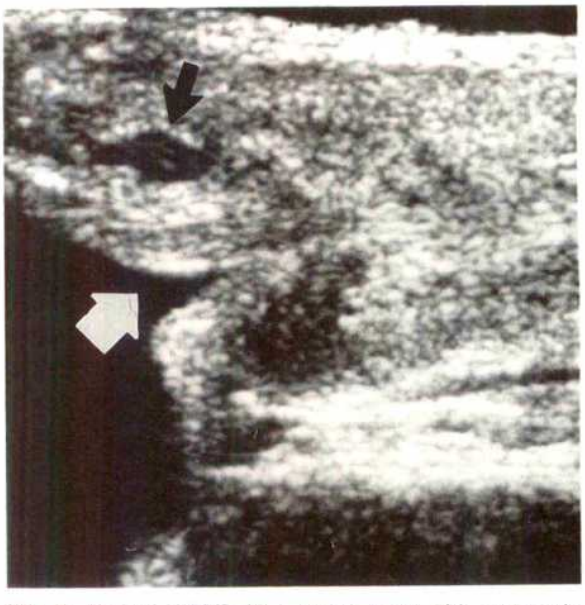

Fig 6 Sagittal TRUS in a young man with retrograde ejaculation. The bladder neck is congenitally incompetent (white arrow). Note the dilated ejaculatory duct (black arrow), cause unknown.

amics. TRUS in the investigation of infertile males is informative and although still in its infancy, with emerging technology the diagnosis of cancer should be possible without biopsy.

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Personal Computers and Urological Research

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Summary—The value of a computer in urological research depends not only upon an appropriate and informed choice of hardware, but also the purchase of software programs which will facilitate input, manipulation and transfer of relevant data. Acquaintance with the Data Protection Act is essential, as is registration as a data user in most cases.

It is well known that research and the preparation of a thesis involves, amongst many other things, the collection and processing of large quantities of data. These then need to be sorted into an easily retrievable order, and usually manipulated statistically and graphically prior to incorporation into a presentation format. This in turn may require repeated modification and correction prior to submission. In all, a vast amount of reduplicated filing, arithmetic and graphical effort will have gone into the finished product.

It is possible to perform all of these tasks on a personal computer (PC). However, the ease and efficiency with which these may be carried out depends initially on the correct choice of equipment and subsequently on the appropriate selection of programs to be installed upon it.

Understanding the Terminology

A personal computer is an expensive collection of electronics at the heart of which is the Central Processing Unit (CPU). This houses a microprocessor, the part which actually does the sums, and in most modern PCs a hard disc on which data and programs may be permanently stored. The CPU has numerous connection sockets (ports) through which it may be connected to various peripheral devices to allow for input or output of data. The most important input device is the keyboard, and the principal output peripherals are a television screen or Visual Display Unit (VDU) to display the information, and a printer. However, information may also be transferred to and from the CPU via floppy discs, telephone lines (modems), computer network links, and directly from other electronic equipment. These physical items comprise the so-called "hardware".

A PC's "memory" may be subdivided into 3 parts. Random access memory (RAM) is an electronic workspace, present only for as long as the machine is turned on. It may be thought of as short-term memory. For data to be retained after the machine is turned off they must be stored, usually in electromagnetic media in the hard or floppy discs. They can then be retrieved as required at a later stage, the equivalent of long-term memory. Read Only Memory (ROM) is a physical characteristic of the computer circuitry. It cannot be deleted or added to, and so to stretch the metaphor could be thought of as the PC's instinct or personality. However, it is relatively unimportant to the average user.

It is only when the PC is given specific instructions, initially as to the language in which it is to think, and then the tasks to perform using this language, that it can function usefully. These instructions are given to the PC by means of "software" programs. The most important of these programs is that which tells the PC how to operate its discs and in particular how to read and write to and from them when given specific instructions. The most popular of these disc operating systems has the trade name "MicroSoft Disc Operating System", hence MS-DOS. Many PCs come pro-

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vided with this operating system, although others are available in this country.

Having given the machine the capacity to understand commands and carry them out, there are many different software programs which can be used. Those which allow the computer to act as a typewriter as well as to store, edit and print the written material are called *word processing* programs. There are several types of word processing software available and some PCs are supplied with their own word processing packages.

A *data base* program is a highly sophisticated collection of instructions which allows the Pc's memory to function as an almost infinite collection of filing cabinets in which data can not only be stored and easily re-indexed but also retrieved and audited. These data may be numerical, alphabetical, or free text.

A *graphics* package enables small groups of figures to be pictorially related, for instance as pie charts, bar graphs, or a host of other graphical modes. In addition to storing and printing of data, a limited amount of mathematical manipulation may be performed.

Statistics packages allow almost any type of statistical analysis to be performed on a given series of figures. Another useful software package is a *spread-sheet*. This not only stores data but also allows repetitive calculations to be performed on long columns of figures, such as squaring a series of individual radii and multiplying by π to give a corresponding column of areas.

Depending on the compatibilities of the hardware and software involved, statistics and graphics packages may be able to import data directly from a data base, obviating the need to duplicate data input. This may be a difficult procedure to learn, but when mastered, is extremely efficient. Recently a number of software packages have been developed which combine the functions of several of the software categories above, allowing data to be automatically transferred between these modes without any interference from the computer operator.

Choosing Your Hardware

Having understood the potential of a computer it is important to decide whether you really need a PC. If word processing is the only requirement then a machine designed solely for this purpose coupled with a high quality printer may represent a better investment. Assuming that data maniputation as well as word processing is required, then the choice of model depends very much on finance, as well as compatibility with any existing hardware.

A PC needs enough short-term memory to load and use programs. A RAM size of 0.6 to 1 megabytes (MB) is sufficient for most programs. The basic requirements of any research system include a hard disc of good capacity: 20 to 40 MB is ample. Systems which have no hard disc and rely on floppy discs for all data storage (double floppy disc or worse still single disc systems) are cumbersome and impractical for any serious research purposes.

Monitors or VDUs come in a choice of monochrome or colour, and sizes usually range between 12 and 14 inch. There seems little point in having a colour graphics package and a monochrome monitor, and a 14-inch screen is definitely easier to work with, especially over long periods. The resolution of the screen is also very important and is determined by the dot pitch, which measures the distance apart of the 3 coloured dots, and hence the clarity of the image. The lower the dot pitch, the higher the quality of the picture and this should be borne in mind when choosing a monitor. A dot pitch of around 0.28 mm gives a high resolution, while only 0.42 mm a much lower resolution.

Printers vary enormously and are available in black and white or colour. Daisy wheel printers have good quality lettering but are not suitable for graphics. Dot matrix printers are very popular and have good graphics capacity. Depending on the model and particularly the number of pins in the printhead, they are suitable for most purposes. A 24-pin printhead gives good quality as well as versatility for most character sets and print fonts found in popular word processing packages. More sophisticated printers employ inkjets to spray the image onto paper, with excellent results, but they are expensive to run and may produce problems with inkjet blockage etc. At present the highest quality is achieved by laser printers, but the disadvantages include slow printing as well as high running costs.

As a rough guide a good quality PC with 20 to 40 MB hard disc, 0.6 to 1 MB RAM and a high resolution 14-inch colour monitor should cost between £1200 and £2500, with several excellent quality machines around £1600. Good letter quality printers start from around £200 with colour options from £450. Prices for paint jet colour printers begin at around £700, but laser printers remain an expensive luxury, with few models below £1000 and colour options being much more expansive than that.

. . . and Your Software

What to look for in software depends largely on the envisaged use. There are too many packages available to list these individually, but as already mentioned, probably the most important feature is compatibility, particularly in the ability to import data from other sources for manipulation or processing. Deciding on software is largely a matter of personal choice and budget. There is no substitute for gaining "hands on" experience either from colleagues or from computer suppliers. Many hospitals now have computer departments able to supply some advice and experience without any commercial bias.

Apart from the price (anything from £50 to £2000+), factors that may influence choice of a database include its structure (how many records will it allow, how large can they be, how many files can be open at once? etc.) and its function (what language mode is used for data queries, can it automatically interrelate data from separate files, *i.e.* a "relational database", will it handle graphics and text as well as data, can it be used on a network system allowing input from more than one user? etc.).

Word processing packages run up to about £400, depending on the sophistication of the features. These largely relate to the format that the printed document will take in terms of style, typeface, etc, and obviously this is ultimately limited by the printer chosen. Other important considerations are the ability to merge documents or files and the graphics capabilities. A built-in spelling checker and thesaurus is also useful.

The choice of statistics and graphics packages is not quite so wide ranging. Most statistics packages will handle data adequately, but their limitations may be seen in their ability to represent the output graphically. Graphics packages may look superficially attractive and colourful, since the principal market for these is in business presentations; however, it is important to remember that in research terms it is more important to be able to present data clearly and scientifically, usually in a monochromatic form, and often scaled down to fit within text columns.

Combination software packages represent the ideal in terms of compatibility but generally do so at the expense of some of the more advanced features of individual software items. In general terms one may expect to spend up to £1000 on setting up the basic software requirements for the average user.

Using It

Having set up this electronic research tool there will be a natural urge to get on with the job, but here a word of caution must be expressed. The *Data Protection Act* (1984) requires that computer users comply with 3 main obligations (Harding, 1986):

(A) To register the use of any personal data with the data protection registrar, including a description of the data and the purpose for which the data are stored.
(B) To acknowledge the rights of individual subjects whose data are stored by the data user. This includes a right of access in an intelligible form, to the data held pertinent to themselves by that subject, as well as rights to compensation for damage or distress should the data be misused, lost, or disclosed inappropriately.
(C) To operate in accordance with the following data protection principles:
   1. Information shall be obtained and preserved fairly and lawfully.
   2. Personal data shall only be held for one or more specified and lawful purposes.
   3. Data held for one specific purpose shall not be used in a manner incompatible with that purpose.
   4. Data held shall be adequate, relevant and not excessive.
   5. Data must be accurate and kept up to date.
   6. Data should not be kept after their original purpose or aim has been achieved.
   7. The individual rights of data subjects (those to whom the data pertain) must be upheld.
   8. Appropriate security measures shall be taken against unauthorised access, disclosure, destruction, or accidental loss or destruction of personal data.

In essence, anyone collecting data concerning patients for whatever purpose must be registered to do this. The penalties for not doing so include imprisonment and unlimited fines. Registration is relatively straightforward and most area health authorities have a data protection officer who will be able to advise further on the specific requirements of the act as it relates to your research. In fact, registration can often be arranged through them as additional data users. From June 1991 the cost of registration will be £75. Further information is available from the *Data Protection Registrar, Springfield House, Water Lane, Wilmslow, Cheshire, SK9 5AX (Tel. 0625 535777).*

Practical Applications

From the foregoing the immediate applications of the computer system in research are obvious. Maintaining logbooks, audit of procedures and outcome, relating these variables and looking for statistically significant trends become virtually automatic. Similarly, presentation of these data is greatly facilitated. Overheads and slides are now easily produced from graphics packages. From the point of view of preparing a thesis, computerisation is becoming something of a necessity, especially with the inevitable shortages and escalating costs of medical secretarial time. All of this could apply in any discipline, but with a little extra kit and a bit of ingenuity the role of the computer can be expanded so that it is taken right into the experimental workface. In this specific regard its use in urological research could include the initial capture and expression of experimental data. For instance, the computer may be connected directly to flow meters and pressure monitors to record urodynamic functions. Video sources such as that used with most modern cystoscopes work on an analogue system; however, "picture digitisers" and scanners are available which allow visual images to be manipulated, enhanced and stored by the computer. The principal example of this is seen with digital subtraction angiography, but urological uses for this type of function could certainly be envisaged.

Despite having no typing skills and being "computer illiterate", most new researchers will find that they can easily master the basics of word processing as well as understand and use the graphics, statistics and data base packages described. Given help and supervision as well as a machine with which to experiment, this may only take a small number of weeks, and within months it is possible to become quite proficient in most of the important functions of the computer and its software.

Anyone considering research lasting for a year or more will benefit from the use of a PC. Similarly, academic departments with ongoing projects, particularly those involving long-term patient follow-up and continual update of patient data, would soon find a sensibly chosen PC for departmental use an indispensable tool.

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Psychological Factors in Recurrent Uncomplicated Urinary Tract Infection

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Summary—Recurrent urinary tract infection (UTI) is a very common medical complaint among women. A large proportion of such recurrence is attributable to a small sub-group of sufferers. Medical factors have proven insufficient to explain all such cases, and a number of psychological factors have been suggested as having a causal role. This study examines the evidence for the effects of behavioural and personality factors. Neuroticism and specific "risky" behaviours are identified as particularly important, being related to both the diagnosis of recurrent UTI and the frequency of infection. These findings suggest that treatment of recurrent, intractable UTI might include a psychological component.

It is widely recognised that urinary tract infection (UTI) is one of the most common infectious diseases encountered in medical practice and that it is a source of frequent GP consultations (Andriole, 1987). UTI is characterised by significant bacterial colonisation of the bladder and is marked by dysuria and by frequency and urgency of micturation. Estimates suggest that 20% of women will experience UTI symptoms in any year and that half of these will seek medical help (Sanford, 1975). These figures are much lower in men, probably due to the protective barrier provided by their longer urethra (Bran *et al.*, 1972). However, these overall incidence figures mask the fact that the number of UTIs is not distributed evenly among the sufferers. There appears to be a small group of recurrent UTI sufferers who account for an unusually large number of reported cases. Mabeck (1972) estimated that one-sixth of sufferers account for 70% of recurrences.

The aetiological factors underlying recurrent UTI are still insufficiently understood. A number of medical correlates are well established, such as the role of bacterial adherence factors (Schaeffer, 1988). However, it is clear that the mechanisms leading to recurrent bacteriuria are not yet fully explained (Fihn and Stamm, 1985). Attempts to treat recurrent UTI within a model of acute infection will inevitably meet with limited success until this understanding is increased. Such women often receive long-term antibiotic treatment, even though this has a number of possible side effects, such as eventual resistance to the specific drug used (Vosti, 1975).

In order to enhance knowledge of the causes of recurrent UTI, several behavioural and personality factors have been investigated. These factors are generally seen as antecedents of UTI, encouraging bacteria to enter and colonise the bladder. However, they might also be maintaining consequences of the infection. There is some preliminary evidence to suggest that these psychological factors can account for some of the unexplained variance in the recurrence of UTI.

Several behavioural factors have been hypothesised to enhance the risk of recurrent UTI (Galland *et al.*, 1977; Adatto *et al.*, 1979). Although the research concerning such factors and UTI is neither extensive nor sophisticated, particular behaviours appear to be relevant. They include low intake of liquid (Ervine *et al.*, 1980), deferred voiding after

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the initial urge to urinate (Adatto *et al.*, 1979), deferred voiding after sexual intercourse (Strom *et al.*, 1987; Fihn, 1988), and frequency of intercourse (Foxman and Frerichs, 1985a). It is also frequently assumed that hygiene habits play a role in recurrence of UTIs, although the evidence for this factor is less substantial. Behavioural intervention studies are limited, but tend to confirm that changing the "risky" behaviours outlined above leads to a lower rate of recurrence of infection (Lumsden and Hyner, 1985).

Research has shown that there are several major personality styles that are associated with recurrent UTI. These styles are within the normal range and do not necessarily reflect any psychiatric disorder. In particular, obsessionality and neuroticism have been described as relevant (Hafner *et al.*, 1977; Rees and Farhoumand, 1977). However, these studies often lack appropriate comparison groups and generally use heterogeneous clinical subjects.

In general, existing studies of psychological factors in the aetiology of recurrent UTI have major limitations. Existing research has generally used either idiosyncratic methodology or inappropriate groups for comparison (*e.g.* students, rather than a normal adult population). Given the results of preliminary studies of psychological intervention in this field of behavioural medicine (Lumsden and Hyner, 1985), it is obvious that more comprehensive psychological research could be of great value in understanding and treating recurrent UTI.

This study considers such psychological factors in the presentation of recurrent UTI, examining behavioural and personality variables. It employs an appropriate clinical group (*i.e.* homogeneous in the diagnosis of recurrent UTI) and a more appropriate comparison group (*i.e.* suffering from a non-urinary tract infection and with no history of UTI).

Patients and Methods

Two groups of subjects were recruited from a large General Practice. All 51 of the subjects who were initially approached were female and were selected through examination of a continuous series of laboratory reports.

In the clinical group, the criteria for recurrent UTI were a positive current laboratory report and a history of at least 2 other such episodes in the past year. The current episode was required to have been defined by a laboratory report showing $>10^5$ organisms/ml of urine. The previous episodes had been diagnosed by the medical practitioner. While the great majority of these previous episodes were accompanied by laboratory reports, a small number were not. Any reported episode of UTI with a laboratory report that fell below the criterion of $>10^5$ organisms/ml of urine was excluded from consideration. Using these criteria, the total number of urinary tract infections that the women had experienced in the previous year was also recorded.

The comparison group were all suffering currently from non-urinary infections (throat infections, fungal infections, or digestive tract infections—confirmed by laboratory report) and had no history of urinary tract infection. The comparison women were also selected to match the marital status and age of the clinical group. The mean ages of the clinical group (mean = 36.5 years, SD = 9.57) and the comparison group (mean = 36.7 years, SD = 8.82) were very similar. However, these ages are substantially higher than the ages of the student populations studied by other researchers (Adatto *et al.*, 1979).

Subjects were interviewed to explain that they were being asked to assist with a study of psychological factors in general health, and to explain how to complete the questionnaires. They were asked to return the questionnaires by reply-paid envelope within 7 days. The response rate was relatively high. Of the 25 women interviewed for the comparison group, 3 failed to return their questionnaires. Of the 26 women interviewed for the clinical group, 3 failed to return their questionnaires and 4 returns could not be scored because of missing data. Thus the clinical group consisted of 19 women with a confirmed history of recurrent UTI and the comparison group consisted of 22 women with no such history.

The behavioural factors were measured using Foxman and Frerichs's (1985b) "Inventory of Habits". This self-report questionnaire contains items relating to behaviours that are assumed to provide some risk of developing urinary tract infection. For the present purposes, a sub-set of the most relevant behaviours was selected on the basis of previous research findings. These behaviours included frequency of urination (per 24 h); delay in urination after the initial urge, frequency of hesitation to excuse oneself from a social setting in order to urinate; frequency of sexual intercourse; frequency of urination within 30 min prior to sexual intercourse; frequency of urination within 15 min after sexual intercourse; frequency of washing the vaginal area within 15 min after sexual intercourse; frequency of bathing. Frequency of showering was also recorded for the present study, using response categories similar to those used by Foxman and Frerichs when enquiring about the frequency of bathing.

The "Inventory of Habits" employs ordinal (ranked) responses, which are not suitable for parametric analysis. Therefore we used non-parametric methods for all statistical analyses involving these measures. More specifically, where the 2 groups were being compared on the Inventory scores, we used the Mann–Whitney test for independent samples. When the Inventory scores were being tested for association with the frequency of UTI, correlations were obtained using Kendall's *tau*. These non-parametric analyses are detailed by Cohen and Holliday (1982).

Relevant personality variables were also selected on the basis of the findings of previous research. The Maudsley Obsessive-Compulsive Inventory (MOC) (Rachman and Hodgson, 1980) was used to measure obsessionality, which was suggested to be relevant by Rees and Farhoumand (1977). The Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck, 1975) was used to measure 2 features that had been suggested by previous research. First, it measures general neuroticism (EPQN), the role of which was highlighted by Hafner *et al.* (1977). Second, it measures extroversion and introversion (EPQE), a dimension that might encompass the tendencies towards "emotional repression" and "withdrawal" that Straub *et al.* (1949) suggested were relevant to disturbed bladder function. The EPQ also measures a third dimension of personality—psychoticism (EPQP)—which is not hypothesised to be relevant to recurrent UTI.

The EPQ and the MOC provide data that are suitable for parametric analyses. Therefore, comparison of the groups on personality measures is carried out using 1-way analysis of variance (ANOVA) for independent groups. The association of personality measures and the frequency of UTI is measured using Pearson's product-moment correlation statistic (r). These parametric methods are detailed by Cohen and Holliday (1982).

Results

The data were considered in 2 ways. First, the qualitative link between psychological factors and a diagnosis of recurrent UTI was addressed by comparing the 2 groups. Second, the quantitative association between psychological factors and the frequency of UTI (in the recurrent UTI group only) was described.

Behavioural factors associated with diagnosis of recurrent UTI

Table 1 shows the results of Mann–Whitney U tests, used to compare the responses of the clinical and comparison group on the different items of the Inventory of Habits. One-tailed tests were used because previous models and research led to the prediction that particular behavioural patterns (rather than general behavioural abnormality) would be associated with recurrent UTI.

Table 1 Mean Ranks of Scores on Inventory, with Comparison of Groups Using 1-tailed Mann–Whitney Tests

	Clinical group ($n=19$)	*Comparison group ($n=22$)*	Z	P
Frequency of urination	19.6	22.3	0.749	NS
Delay before urination	19.8	22.1	0.675	NS
Hesitation to excuse self to urinate	20.4	20.6	0.057	NS
Frequency of sexual intercourse	23.3	18.2	1.460	NS
Urination prior to sexual intercourse	24.1	17.6	1.841	0.04
Urination following sexual intercourse	20.8	19.3	0.409	NS
Washing following sexual intercourse	18.9	22.0	0.846	NS
Frequency of bathing	17.7	23.8	1.756	0.04
Frequency of showering	22.2	20.0	0.623	NS

As can be seen, there was relatively little difference between the groups on most of the Inventory responses. However, there were reliable differences on 2 of the 9 behaviours. The clinical group were significantly more likely to urinate prior to sexual intercourse, and took fewer baths than the comparison women. Both behavioural differences were in the direction predicted from previous research.

Personality factors associated with diagnosis of recurrent UTI

Table 2 shows the mean scores of the 2 groups on the measures of personality, and the results of 1-way ANOVAs comparing the groups' scores. Again, 1-tailed tests were used for most of the comparisons because previous research suggests that the clinical group will be more obsessional, neurotic and introverted than the comparison

Table 2 Mean Scores on Personality Measures, with Comparison of Groups Using 1-tailed ANOVAs

	Clinical group ($n=19$)	*Comparison group ($n=22$)*	*F*	*P*
MOC	8.58	6.10	2.98	0.05
(SD)	(4.69)	(4.27)		
EPQN	14.1	11.2	3.28	0.04
(SD)	(4.15)	(5.89)		
EPQE	11.3	14.3	4.73	0.02
(SD)	(5.13)	(3.16)		
EPQP	3.05	2.70	0.43	n s
(SD)	(1.96)	(1.38)		

MOC: Maudsley Obsessive-Compulsive Inventory.
EPQN: Eysenck Personality Questionnaire (general neuroticism).
EPQE: Eysenck Personality Questionnaire (extroversion and introversion)
EPQP: Eysenck Personality Questionnaire (psychoticism).

women. However, a 2-tailed test was applied to the psychoticism scale, where there was no predicted difference.

The clinical group showed significantly greater degrees of obsessionality (MOC), neuroticism (EPQN) and introversion (lower EPQE score), each of which had been predicted by or hypothesised from previous research. There was no difference on the psychoticism scale (EPQP), suggesting that the groups were not simply characterised by generally "pathological" and "normal" personalities, but that the differences were specific ones.

Association of frequency of UTI with behavioural and personality variables

The frequency of UTI in the clinical group was associated with 4 of the 9 behavioural factors. It was positively correlated (Kendall's *tau*) with the degree of hesitation to excuse oneself to urinate ($\mathit{tau}=0.39$; $P<0.025$), likelihood of urination prior to intercourse ($\mathit{tau}=0.38$; $P<0.05$) and the likelihood of washing following intercourse ($\mathit{tau}=0.42$; $P<0.025$). It was negatively correlated with the frequency of showering ($\mathit{tau}=-0.40$; $P<0.025$). The other behavioural variables were not significantly correlated with the frequency of UTI. To summarise, a higher number of UTIs over the previous year was associated with hesitating to excuse oneself to urinate, urinating before intercourse, washing after intercourse, and showering infrequently.

In contrast, the frequency of UTI was associated with only 1 of the 4 personality variables. It was positively correlated with neuroticism (Pearson's $r=0.39$; $P<0.05$), but the correlation with the other 3 scales did not approach significance. Therefore, a higher number of UTIs over the previous year was associated with a more "neurotic" personality type.

Discussion

This study has considered the roles of behavioural and personality variables in recurrent uncomplicated UTI, using relatively homogeneous clinical and comparison groups. The results have confirmed that a number of general personality styles and specific behaviours differ across the 2 groups. There is also evidence that the frequency of particular behaviours and that a "neurotic" personality type are associated with the frequency of UTI.

Some of the behavioural and personality factors identified as important in previous research were not relevant in this study. There are a number of methodological factors that might explain this difference. First, the relatively small size of the present sample may have reduced the likelihood of finding genuine differences between the groups. Alternatively, the use of relatively homogeneous groups in this study may have reduced the likelihood of finding artefactual differences between the groups. It is also possible that the self-report measure of "risky" behaviours is less sensitive than other measures, such as diary recording. Future research might address these possible reasons for the emergence of particular behaviours and personality styles as high-risk in this study.

These results confirm that there are psychological factors that are important in explaining some of the variance in who develops recurrent UTI and how often infections occur. Of course, it is not possible to make causal statements from these associations. However, the results of intervention studies (Lumsden and Hyner, 1985) suggest that these factors act in at least a maintaining role.

In treating any case of recurrent UTI where purely physical factors are not sufficient to account for the presence or severity of the symptoms, the urologist may wish to address possible psychological maintaining factors. It might be particularly valuable to arrange specific behavioural training for reducing the "risky" behaviours that are associated with the number of UTIs and the diagnosis of recurrent UTI. However, such recommendations can only be made cautiously at present. More definite guidelines await the replication of these results with a larger sample, and the results of psychological intervention programmes aimed specifically at the relevant personality and behavioural variables.

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Extracorporeal Shock Wave Lithotripsy with the Storz Modulith SL20: the First 500 Patients

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Summary—Our initial experience of extracorporeal shock wave lithotripsy (ESWL) with the Storz Modulith SL20 is reported. A total of 500 patients with 551 renal and 120 ureteric stones, mean diameter 11.9 mm, underwent 746 treatments; 68.2% of patients required a single treatment. The mean treatment rate for renal calculi was 1.4 and for ureteric calculi it was 1.5, rising to 4.2 for staghorns; 62.2% of treatments were performed on an out-patient basis. Analgesia (intravenous fentanyl) was required in 60.9% of treatments for renal calculi but in only 38.2% of those for ureteric calculi. The overall stone-free rate at 3 months was 77.6%, with a further 14.7% of patients having fragments <3 mm in diameter that required no further treatment. The stone-free rate was dependent on the site of the stone, with the majority of residual fragments lying in a lower pole calix. There were few complications. The Modulith is an efficient and safe lithotripter capable of treating stones in the kidney and throughout the ureter.

Since its introduction in 1980 (Chaussy *et al.*, 1980), ESWL has become established as the treatment of choice for most types of urinary calculus disease. Clinical advance has been in parallel with technological developments in shock wave generation and delivery and in imaging, with a variety of lithotripters now available. The Storz Modulith SL20 is the most recent addition and has been referred to as a "third generation" lithotripter (Rassweiler *et al.*, 1990).

The stone centre at St Thomas' Hospital was opened in 1985 following installation of the Dornier HM3 lithotripter. Since that time 7500 patients have had urinary calculi treated by ESWL. In January 1990 a Storz Modulith SL20 was also installed. We present our initial experience of this machine following treatment of the first 500 patients.

Patients and Methods

Between January 1990 and January 1991, 500 patients were treated on the Modulith. Their characteristics are shown in Table 1. In all, 311 patients (62.2%) were treated as out-patients, 96 (19.2%) as in-patients and 93 (18.6%) as inter-hospital transfers for the day of treatment. The patients treated included 24 (4.8%) considered unsuitable for day case general anaesthesia and complicating medical factors included ischaemic heart disease (10), recent cerebrovascular accidents (4), severe chronic obstructive airways disease (3), renal failure (3) and insulin-dependent diabetes (3).

The Storz Modulith generates shock waves from an electromagnetic source; these are reflected by a 40-cm parabolic dish, resulting in a treatment focus 6 mm in diameter and 28 mm in depth, at 15 kV (Rassweiler *et al.*, 1990). The Modulith has variable power settings (1–9, corresponding to 11–21 kV). Stone imaging is possible using in-line ultrasound and/or conventional X-ray mounted on a C-arm. These features have been described by Rassweiler *et al.* (1990). Imaging of stones is therefore possible throughout the urinary tract and the study group included 2 patients with renal transplants. The X-ray facilities include image magnification during screening and conventional cassette films may be taken if required. Ultrasound was used as the sole imaging technique in approximately 12% of patients. Where the data were available, mean X-ray

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Read at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

Table 1 Details of Patients (n = 500)

Age (years)		*Sex*		*Side*				*No. of stones*	
Mean (±SD)	*Range*	*Male (%)*	*Female (%)*	*Left*	*Right*	*Bilateral*	*Transplants*	*Treated*	*Range*
50 ± 14.5	17–85	331 (66.2)	169 (33.8)	274	210	16	2	671	1–11

screening time was 96 ± 57 s (mean ± SD; n = 343, range 10–340) with a mean of 7.4 ± 5.3 snapshots (range 0–16). In 8 patients (1.6%) radio-opaque contrast was used to assist imaging of ureteric calculi.

Stones

Five hundred patients had 671 stones with a mean stone size of 11.9 ± 7.0 mm (range 1–58). The distribution of the stones with respect to size is shown in Figure 1 and their distribution according to site within the urinary tract is shown in Figure 2. A total of 411 patients had a solitary urinary calculus (including 1 with a complete and 8 with partial staghorn calculi) and 89 patients had multiple calculi. In 38 cases the multiple calculi were at a single site and in 51 the stones were at multiple sites. In the latter group 16 patients had bilateral stone disease.

Treatment

Renal and upper ureteric calculi were treated with the patients supine and for stones in the mid and lower ureter the patients were placed in a prone position. Shock waves were given at a rate of 1.5 to 2 Hz; this was independent of the ECG unless significant ventricular pacing occurred. In general, treatment to renal calculi consisted of 3000 shocks at a maximum power level of 7 and ureteric calculi received 3500–4000 shocks at a maximum power level of 8. The overall mean number of shocks was 2647 ± 687 (range 300–4000). Treatments were started at the lowest power level without analgesia and the power was increased every 10–20 shocks until the desired level had been achieved or until the patient experienced pain, when intravenous analgesia was administered, by titration of 25–50 μg aliquots, until the desired power level was achieved. Immediately following treatment a plain abdominal radiograph (KUB) was obtained to assess fragmentation. The overall time per treatment was 59 ± 21 min, with a significant reduction in treatment time between the first and last 100 patients from 73 ± 21 to 52 ± 18 min respectively (paired *t* test; $P < 0.001$).

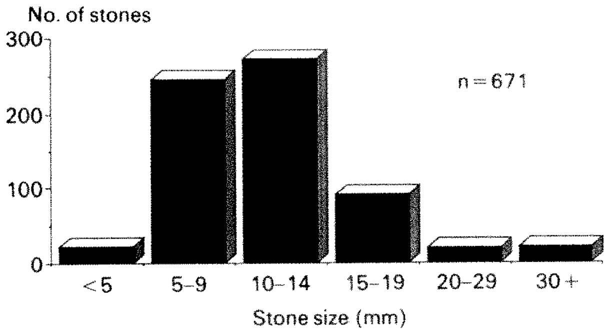

Fig. 1 Distribution of stone sizes.

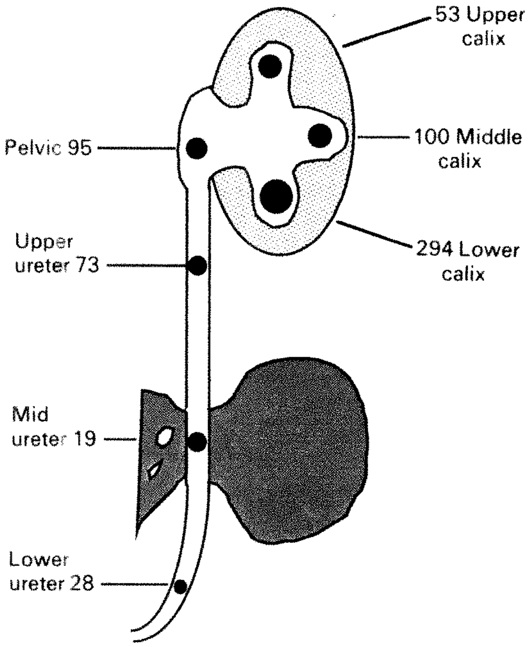

Fig. 2 Schematic representation of urinary tract showing distribution of stones.

Analgesia

Intravenous Fentanyl was used to provide analgesia. The analgesic requirements during treatment of renal and ureteric stones are illustrated in Figure 3. General anaesthesia was employed in 13 treatment sessions (1.7%) only where stone manipulation was required immediately prior to lithotripsy.

Ancillary treatment (before ESWL)

A total of 81 patients (16.2%) were treated with a stent *in situ* and 14 (2.8%) had required nephrostomy drainage prior to lithotripsy; in 6 of these a stent was inserted prior to lithotripsy.

Follow-up

Of the 500 patients, 36 (7.2%) were lost to follow-up. Thus complete follow-up data, to 3 months, were available in 464 patients (92.8%). Patients' stone status was assessed as follows: stone-free: no radio-opaque fragments present on a KUB or ultrasound; adequate fragmentation: residual stone fragments <3 mm in diameter not requiring further treatment; inadequate fragmentation: residual stone fragments >3 mm in diameter and/or fragments requiring alternative treatment.

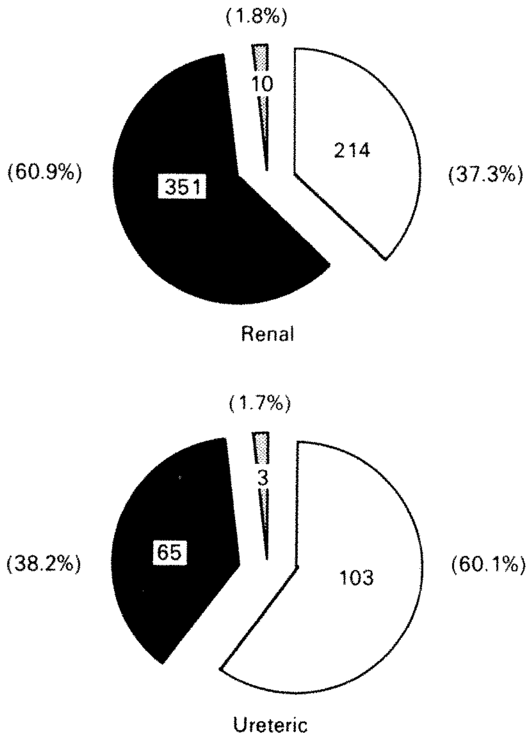

Fig. 3 Differences between analgesic requirements during 574 treatment sessions for renal calculi and 172 for uretric calculi. (black, IV analgesia; white, nil analgesia; grey GA).

Results

This series of 500 patients underwent 746 treatment sessions, giving an overall treatment rate of 1.5 (range 1–6); 341 patients (68.2%) required a single treatment only. The number of treatment sessions per patient is shown in Figure 4. The treatment rate was related to the stone site (Table 2) and the stone size (Fig. 5). The maximal stone size correlated with the number of treatments required (Table 3).

Of the 464 patients with complete follow-up data, 360 (77.6%) were stone-free and 68 (14.7%) had adequate fragmentation, with residual fragments <3 mm in diameter considered not to require further treatment. This gave an overall satisfactory outcome in 428 patients (92.3%). The results were related to the anatomical site of the stone (Fig. 6). The 2 transplant patients were stone-free and had no detectable change in renal function.

Inadequate fragmentation of calculi was observed in 36 patients. This occurred during the first 3 months' experience of the machine, when treatment was curtailed for pain, resulting in inadequate power levels (16/36). The other factors included a large fragment resulting in ureteric obstruction (8), the presence of a "hard stone" (8) and a variety of reasons (including intractable itching) (4).

Complications

There were few serious complications. However, 7 patients (1.5%) developed sepsis requiring intravenous antibiotics, 2 (0.4%) developed an haematoma and 51 (11%) had renal colic following lithotripsy. Renal colic was associated with the presence of either a Steinstrasse or a relatively large stone fragment in the ureter; all of these patients required admission to hospital. The fragment passed spontaneously in 17 patients and was removed using a Dormia basket in 12 and ureteroscopy in 10. In a further 12 patients the fragment was pushed back into the kidney and treated, for logistical reasons only, on the Dornier HM3. None required percutaneous nephrostomy drainage. The complication rate was 12% overall.

Discussion

The provision of 2 lithotripters at this hospital provides a unique opportunity to compare the performance of the first "third generation" lithotripter with that of the Dornier HM3—the accepted "gold standard". Although no formal quantitative

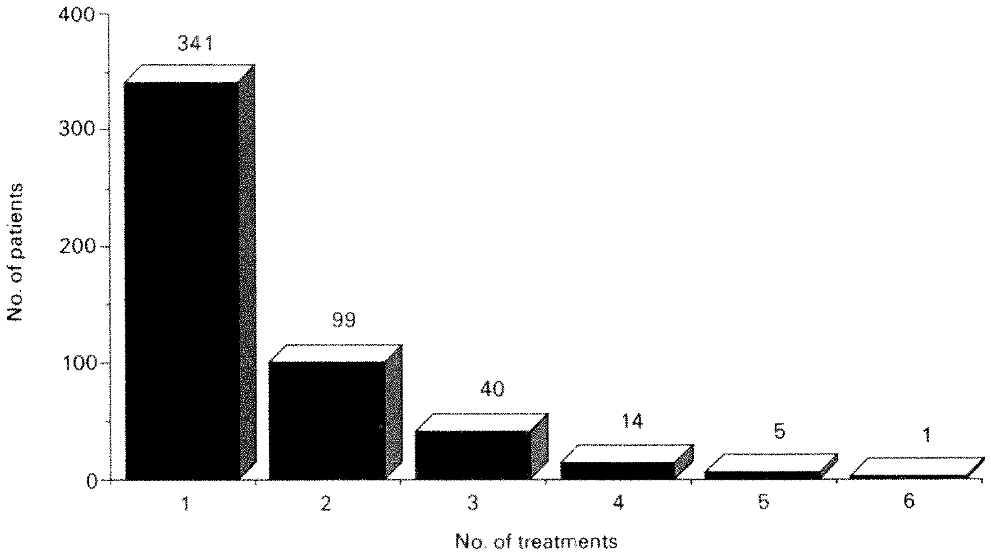

Fig. 4 Number of treatments per patient.

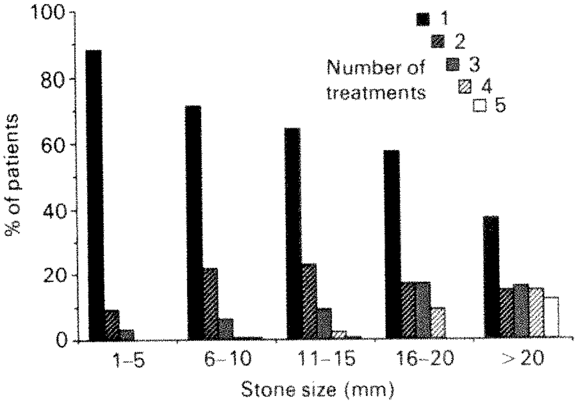

Fig. 5 Relationship between maximum stone diameter and number of treatments required, expressed as a percentage of patients in each group.

comparison has yet been undertaken, a number of qualitative observations may be made.

The dual stone localisation facility of the SL20 allows imaging of lucent renal and biliary calculi and real-time imaging of the stone during treatment. The combination of both imaging modalities permits radiological confirmation of ultrasound images, which greatly increases operator confidence during the learning curve required for the interpretation of ultrasound. The X-ray definition obtained from the SL20 is objectively superior to the Dornier and the facility to magnify the X-ray image is useful to target small calculi.

Table 2 Treatment Rate According to Site

	No. of patients	*No. of treatments*	*Mean rate*
Staghorn	9	38	4.2
Renal	378	536	1.4
Ureteric	113	172	1.5
Overall	500	746	1.5

Table 3 Relationship between Number of Treatments per Patient and Mean Maximal Stone Size

No. of treatments	*Maximum stone size (mm) (±SD)*	*No.*
1	10.6 ± 4.7	341
2	12.1 ± 6.9	99
3	15.4 ± 10.4	40
4	23.7 ± 15.2	14

There was a statistically significant difference between each group (2-tailed *t* test; $P < 0.05$).

The long focal depth (up to 15 cm) allows stone targeting with minimal contortion of the patient and permits treatment of stones throughout the upper urinary tract. Although it is possible to use the Modulith SL20 for endourological procedures, this was not undertaken routinely because a separate procedures room was available.

The results of treatment compare favourably with those of other centres (Sofras *et al.*, 1988;

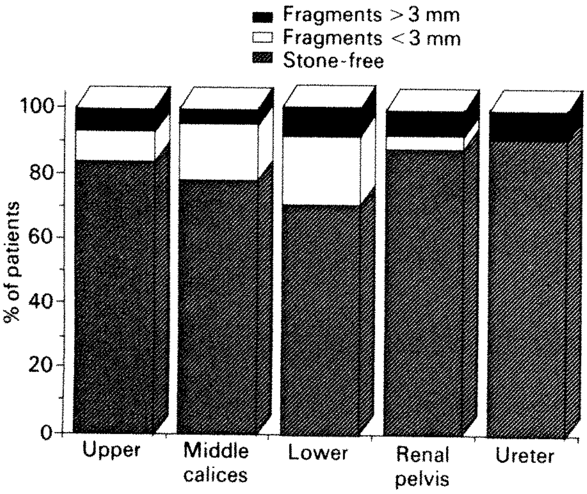

Fig. 6 Relationship between anatomical site of the stone and the stone status expressed as a percentage of the grouping as a whole.

Grace *et al.*, 1989; Tailly, 1990) and other lithotripters and are an improvement on our initial experience with the HM3 (Palfrey *et al.* 1986). Among the advantages of using the SL20 are the high proportion of day case treatments (62%), which represents a significant saving in costs. This high proportion is due to the lack of requirement for general anaesthesia. Furthermore, some patients had significant medical conditions which would have precluded treatment on the Dornier HM3.

The smaller treatment focus of the SL20, by reducing the volume of renal parenchymal damage, might reduce the possible risk of late onset hypertension, which still remains an unanswered criticism of the technique (Holmes and Whitfield, 1991). The small treatment focus could, in theory, result in an increased treatment rate for small calculi, since any error in targeting might result in the stone lying outside the reduced blast path. There was no apparent increase in the treatment rate for such calculi, *i.e.* those less than 1 cm. The overall treatment rate was higher than that reported for the Dornier HM4 or MPL9000, but the mean stone size was large and some of our patients had multiple calculi at different sites (10.2%), which would tend to increase the number of treatments. Furthermore, those with bilateral stone disease (3.2%) would require more than one treatment, as we do not treat both sides simultaneously.

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Percutaneous Nephrolithotripsy for Renal Stones in over 1000 Patients

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Summary—Over a period of 5 consecutive years, 1039 renal units were treated by percutaneous nephrolithotripsy for stone disease of the kidney. The success rate was 93.7%. Residual stones remained in 4.2% of patients and in 2.1% we failed to remove the stones. The complication rate was 17.8%. Complications were treated conservatively in most cases but nephrectomy was required on one occasion to control severe bleeding. The average hospital stay was 6.9 days.

Follow-up of 339 renal units (333 patients), for a minimum of 60 months, revealed minor late sequelae such as pelviureteric junction obstruction in 1 patient (0.3%) and post-catheterisation strictures of the anterior urethra in 4 (1.2%). Stone recurrence was observed in 9.1% of patients.

Percutaneous nephrolithotripsy is an effective, safe treatment for renal stones with minimal late sequelae and is still required even in the era of extracorporeal shock wave lithotripsy.

The management of upper urinary tract calculi has undergone a dramatic change following the introduction of percutaneous nephrolithotomy (PCNL) and extracorporeal shock wave lithotripsy (ESWL). Goodwin *et al.* (1955) described the percutaneous establishment of a nephrostomy tract with a trocar into a hydronephrotic kidney. The first percutaneous tract created specifically for the removal of a stone was reported by Fernstrom and Johansson (1976). By the early 1980s the development of instruments designed to operate through such tracts permitted percutaneous techniques to evolve to a point where, at least theoretically, any stone could be removed from the urinary tract with an acceptable degree of morbidity (Alken *et al.*, 1981; Segura *et al.*, 1983). Today, despite the pervasiveness of shock wave lithotripsy, percutaneous stone removal remains the procedure of choice in many clinical situations and a viable alternative in others. We present our experience with percutaneous nephrolithotomy in more than 1000 patients, with special emphasis on long-term results and complications.

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Patients and Methods

Over 5 consecutive years (1984–1989), 4000 patients with renal stones were treated at this centre; 1024 of these patients (25.6%) were treated by percutaneous nephrolithotripsy; 742 were male and 282 were female. Their ages ranged between 9 and 76 years (mean 42.0 ± 11).

The stones were on the right side in 464 patients, on the left in 545 and bilateral in 15; 1039 renal units were thus treated. The site of the stones is indicated in Table 1.

The stones were single in 767 cases (73.9%), multiple in 272 (26.1%) and recurrent in 333 (32%). Most of the stones were radio-opaque, and were radiolucent in only 27 patients (3.8%).

Fifty-three patients had a solitary kidney. Abnormal renal morphology (seen in 30 patients)

Table 1 Distribution of Renal Stones

Site	*No. (%)*
Pelvis	790 (76.0)
Caliceal	65 (6.3)
Pelvicaliceal	178 (17.1)
Branching	6 (0.6)

included horseshoe kidney in 10, malrotation in 15 and a duplex system in 5.

Puncture was carried out in the radiology suite under local anaesthesia. The kidney was opacified by intravenous urography or by retrograde pyelography. Precise anatomical puncture through the proper calix was controlled by biplane fluoroscopy. This was of particular importance in patients with abnormal renal morphology (Fig. 1). A flexible J guide wire was then threaded down the sheath of the needle and either guided down the ureter or coiled in the upper calix. In recurrent cases a stiff guide wire (Lunderquist-exchange guide wire) was preferable to avoid bending during dilatation. Malleable fascial dilators were subsequently passed over the wire, dilating the tract to 10–12 F. This was followed by fixation of an 8–10 F pigtail catheter. In the majority of cases, definitive dilatation of the tract and nephroscopy were carried out within 24 to 48 h. In 362 cases (35%) the whole procedure was completed on the same day.

Definitive dilatation of the tract and lithotripsy were carried out in the endoscopy suite under general or spinal anaesthesia. The technique was a standard one as described by Alken (1982) and Marberger (1983). The tract was dilated to 32 F with fixation of an Amplatz sheath. Glycine was used for irrigation at a head pressure of 60 cm H_2O. The patients were infused with 12 g mannitol to protect the kidney from pyelotubular backflow. Small stones were removed by forceps. Combined ultrasound disintegration and mechanical extraction was employed for larger stones. The entire procedure was carried out under fluoroscopic control.

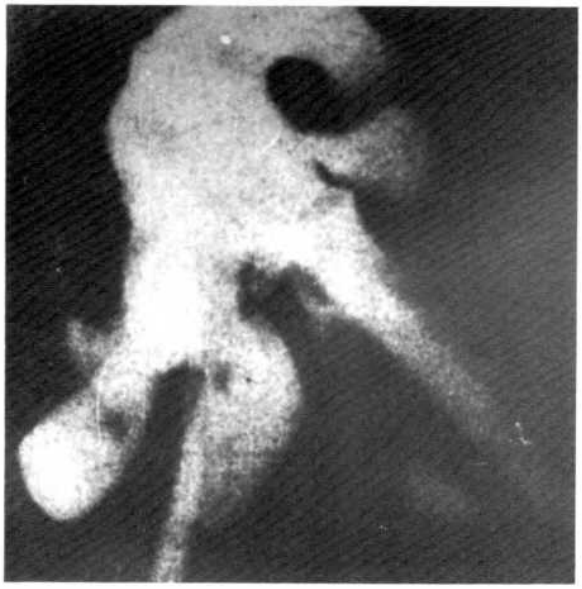

Fig. 1 Placement of percutaneous tract in horseshoe kidney.

Following removal of the stones a 22F nephrostomy tube was inserted through the sheath of the endoscope to the renal pelvis. A control X-ray and an antegrade study were performed to ensure complete removal of the fragments and to exclude any extravasation. This tube was removed when the drainage became clear, usually within 2 to 3 days.

In all, 333 patients were followed up for a minimum period of 60 months. A thorough physical examination, measurement of blood pressure, urine analysis, urine culture, intravenous urography and renal ultrasonography were carried out. Digital vascular imaging was indicated whenever there was clinical evidence of hypertension of recent onset.

Results

Complete removal of the stones was achieved in 973 of 1039 renal units, a success rate of 93.7%. Complete clearance was possible in one session in the majority of cases (79.8%) but some patients required 2 or 3 sessions to remove residual stones or gravel following ultrasound disintegration.

Radiological evidence of residual stones was seen in 44 patients (4.2%). In a further 22 cases it was not possible to remove the stones because of failure to establish good access (5 patients) or inability to visualise the stone during endoscopy (17).

Complications included those inflicted during puncture, during definitive endoscopy or during the post-operative period.

Creation of the percutaneous tract was associated with 42 complications (Table 2). All were conservatively managed and did not interfere with further nephroscopic manipulation. Fracture of the guide wire was seen in 5 cases (Fig. 2). This was encountered during difficult dilatation of recurrent

Table 2 Complications Following Puncture

Complications	*No.*
Pelvic tear	20
Bleeding	12
Septicaemia	5
Fractured guide wire	5
Total	42 (4%)

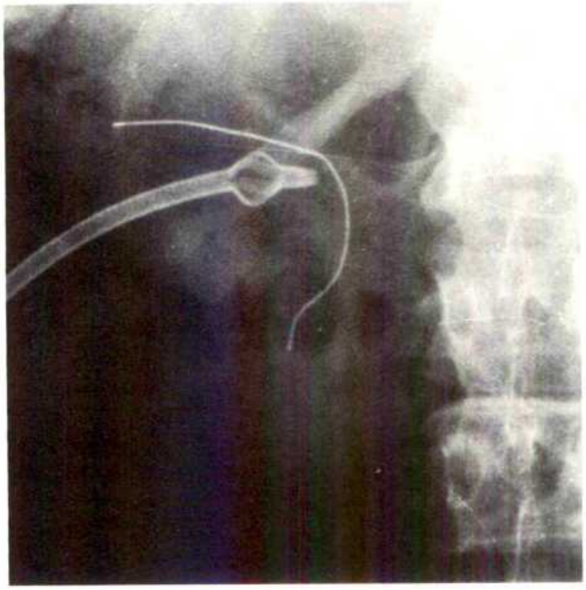

Fig. 2 Plain X-ray showing fractured guide wire during creation of a percutaneous tract.

fibrous tracts and the guide wires were later mechanically extracted during nephroscopy.

Of the complications encountered during nephroscopy, the most frequent was pelvic tear (31 patients) and this was treated by nephrostomy drainage. Sixteen patients required a transfusion because of per-operative bleeding. A supracostal approach to remove a stone in a high-lying kidney resulted in hydrothorax in 1 patient. This was treated conservatively by nephrostomy and chest drainage. Colonic perforation was encountered in 4 patients (Fig. 3), all of whom underwent successful conservative treatment consisting of drainage of the pelvis by a wide ureteric catheter, nasogastric suction, administration of a broad spectrum antibiotic as well as anal dilatation (Lord's manoeuvre) to avoid build-up of pressure in the large intestine. The ultrasound probe was fractured in 1 case and the forceps in another.

Post-operative bleeding from the nephrostomy tube, or haematuria after its removal, was observed in 34 patients. Five required blood transfusion and were conservatively treated. Three required radiological intervention with embolisation. This procedure was successful in 2 cases (Fig. 4), but nephrectomy was necessary in the third. Post-operative pyrexia was recorded in 55 patients and they were treated with the appropriate antibiotic.

No mortality was reported in association with the procedure. The average hospital stay was 6.9 days.

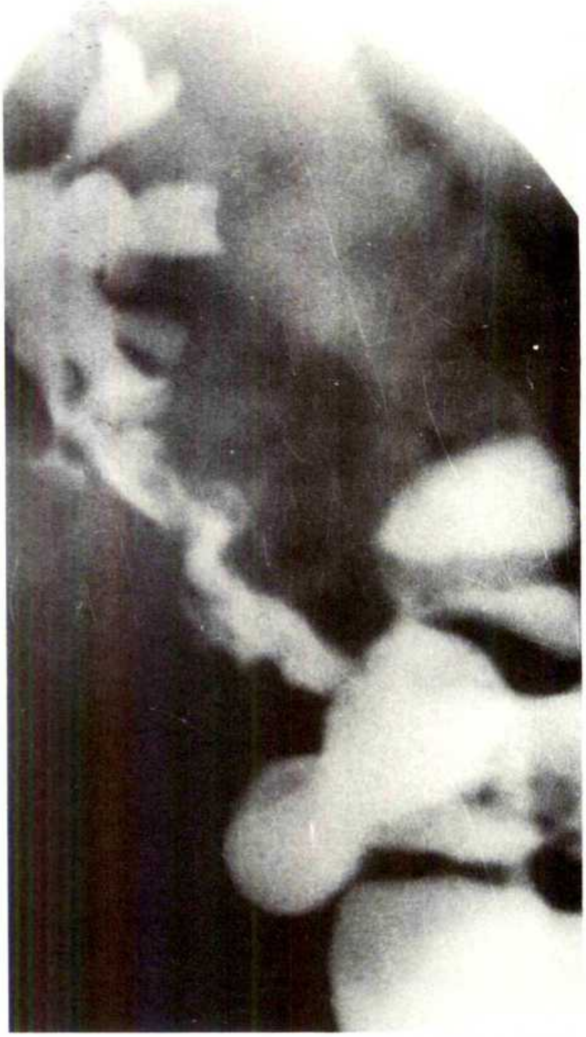

Fig. 3 Renocolonic fistula inflicted during percutaneous nephrolithotripsy.

Of the 333 patients with a minimal follow-up of 5 years, stone recurrence was documented in 31 (9.1%). Of these, 70% had a past history of recurrent renal stones on the same side. Sixteen patients (4.8%) were discharged with small fragments after initial therapy. These were judged to be surgically insignificant. Spontaneous passage of these fragments was documented in 7 cases and 6 remained unchanged. In 3 cases the residual stones increased in size and were later treated by ESWL.

Four patients developed post-catheterisation stricture of the anterior urethra; this was managed

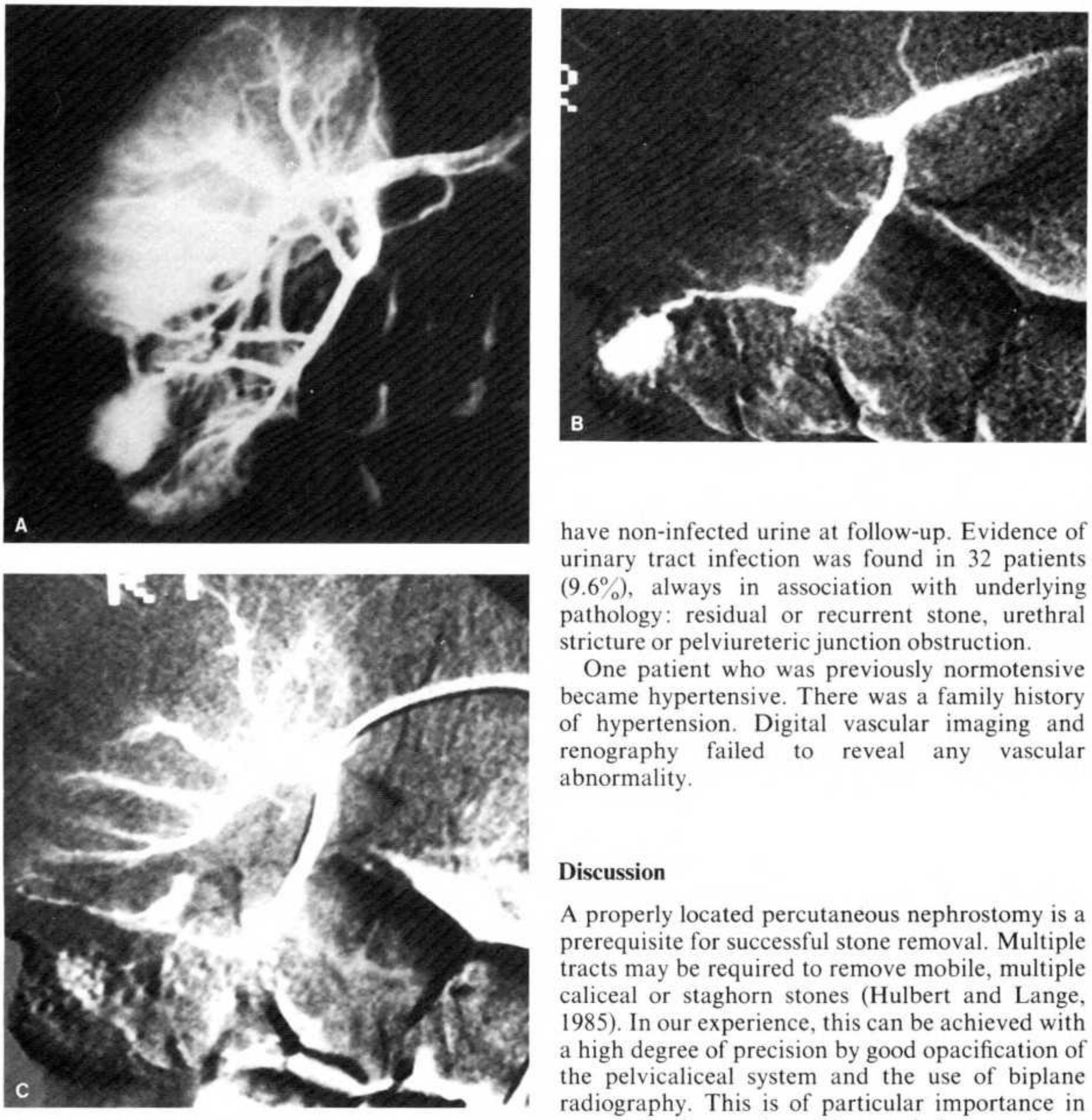

Fig. 4 (A). Selective renal arteriography showing extravasation of dye from an injured lower polar artery. (B). Selective embolisation of the injured artery. (C). Selective renal arteriography after embolisation showing no blood flow through the injured artery.

by visual internal urethrotomy. Obstruction of the pelviureteric junction was reported in 1 patient with a solitary kidney and this was corrected by an endopyelotomy.

All patients whose urine was sterile pre-operatively, and who were free of stones, continued to have non-infected urine at follow-up. Evidence of urinary tract infection was found in 32 patients (9.6%), always in association with underlying pathology: residual or recurrent stone, urethral stricture or pelviureteric junction obstruction.

One patient who was previously normotensive became hypertensive. There was a family history of hypertension. Digital vascular imaging and renography failed to reveal any vascular abnormality.

Discussion

A properly located percutaneous nephrostomy is a prerequisite for successful stone removal. Multiple tracts may be required to remove mobile, multiple caliceal or staghorn stones (Hulbert and Lange, 1985). In our experience, this can be achieved with a high degree of precision by good opacification of the pelvicaliceal system and the use of biplane radiography. This is of particular importance in cases of abnormal renal morphology such as malrotation, a horseshoe kidney or a duplex collecting system. Alken *et al.* (1981) suggested ultrasound-guided puncture. This may prove difficult in non-dilated systems and there remains the need for subsequent X-ray for placement of the guide wire and control of the dilatation.

Staging the procedure would prolong the hospital stay by 24 to 48 h, although subsequent dilatation and visualisation would then be easier. It would also allow readjustment of the tract (if required) before embarking on the definitive procedure. Wickham *et al.* (1984) reported that a one-stage procedure would necessitate a second session in 20% of patients because of failed puncture, perforation or poor visualisation. Nevertheless, a one-stage procedure could be adopted when sufficient experience in the technique has been gained and it is mandatory when only an unstable tract can be established, as in cases of peripheral caliceal stones where it is often difficult to thread the guide wire into the major collecting system.

Failure of access, resulting in failure to remove the stones, was reported in 1.7% of patients by Segura *et al.* (1985), in 8% by Whitfield and Mills (1985) and in 6.4% by Jones *et al.* (1990). In our series the failure rate was 2.1%.

Post-operative complication rates ranged between 3.2% (Segura *et al.*, 1985) and 13.2% (Jones *et al.*, 1990). This wide variation probably reflects different methods of reporting. In the present series the rate was 8.6%. The most common complication following the procedure was bleeding. In most cases it is minor and does not require transfusion. Blood transfusion was necessary in 21 of our patients (2%), a figure which compares favourably with the 3% reported by Segura *et al.* (1985) and 5.8% by Jones *et al.* (1990). Angiographic embolisation for an arteriovenous fistula was necessary in 3 patients (0.3%). Segura *et al.* (1985) and Jones *et al.* (1990) reported that this was necessary in 0.6 and 0.4% of their patients respectively.

In this series, the incidence of residual fragments was 4.2%. Comparable results have been reported by White and Smith (1984) (2.5%), Brannen *et al.* (1985) (2.8%) and Segura *et al.* (1985) (8.1%).

The number of staghorn stones treated by percutaneous surgery in this series was limited. We prefer open surgery (extended pyelolithotomy with or without radial nephrotomy) for the management of these patients. This is because complete stone removal is almost guaranteed with open surgery, particularly when "on table" X-rays are taken. When staghorn stones were treated by percutaneous surgery alone the reported incidence of residual fragments ranged between 16% (Segura *et al.*, 1985) and 23% (Eisenberger *et al.*, 1987). When percutaneous nephrolithotripsy was combined with ESWL, the incidence of residual stones was reported as 21.5% by Schulze *et al.* (1986), 40% by Eisenberger *et al.* (1987) and 77% by Segura *et al.* (1987). These procedures tend to prolong the hospital stay and are associated with higher costs than open surgery (Di Silverio *et al.*, 1990).

The incidence of stone recurrence following this procedure among patients who were followed up for 5 years was 9.1%. This is similar to the 10% reported by Segura (1989). Iatrogenic pelviureteric junction obstruction following percutaneous nephrolithotripsy was observed by Hidalgo *et al.* (unpublished observations), who reported an incidence of 0.9%. We noted this complication in 1 patient (0.3%). A possible cause is injury during the course of stone manipulation. Endopyelotomy provides a logical and uncomplicated method of managing this complication. We encountered no case of hypertension which could be attributed to the procedure. Marberger *et al.* (1985) made a similar observation.

Despite the installation of an ESWL machine in this centre, we still perform open surgery and percutaneous nephrolithotripsy in approximately one-third of patients with stones. This is significantly higher than the proportion reported in Europe and America (Chaussy and Fuchs, 1989), who claimed that open sugery was required in less than 5% of their patients. This was due to the larger bulk of stones and/or associated pathology requiring surgery. There is no doubt that the frequency of percutaneous surgery for stone disease will diminish with the adoption of ESWL. Nevertheless, the procedure will still be indicated in some instances: large stones >3 cm, stones in a calix or caliceal diverticulum, stones with pelviureteric obstruction and branching stones. In other words, endoscopic manipulation will be required for the more difficult stones, as reported by Jones *et al.* (1990), who observed that the post-operative complication rate for percutaneous stone surgery increased from 13.6 to 24% after the introduction of ESWL. Thus the treatment of renal stone disease by percutaneous surgery is a technique which should not to be forgotten but has to be perfected. Furthermore, in developing countries it will be some time before treatment with ESWL becomes widely available, and percutaneous nephrolithotripsy will remain the method of choice for a significant proportion of renal stones.

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Hydatid Disease of the Urinary Tract: Evaluation of Diagnostic Methods

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Summary—Eight patients with histologically proven hydatid disease of the urinary tract underwent eosinophil count, ultrasonography (US) and computed tomography (CT). The findings were compared with those in 8 age-matched controls with simple renal cysts. Eosinophilia was not significantly different in the 2 groups. Mixed echogenicity on US and multivesicular cyst with mixed density on CT were the diagnostic features of hydatid cysts. Using these factors, both US and CT could diagnose or exclude hydatid disease in a significant number of patients with renal cysts. However, CT was more sensitive (88 *vs* 50%) and accurate (94 *vs* 75%) than US in the diagnosis of urinary tract hydatid disease. Retrograde pyelography confirmed communicating renal hydatid cysts in 2 patients. A practical algorithm for the investigation of urinary tract hydatid disease is suggested.

Hydatid disease or echinococcosis is a cyclozoonitic parasitic infestation that is endemic in parts of Africa, Australia, New Zealand, South America, North America, Greece and Spain (Saidi, 1976; Golematis, 1978; Gilsanz *et al.*, 1980; Benchekroun *et al.*, 1986). In the Middle East, many cases have been reported from Iran, Iraq, Syria and Jordan, where the disease is endemic (Saidi, 1976; Dajani, 1978; Halim and Vaezzadeh, 1980; Al-Ani and Al-Waili, 1986).

The Asir region of southwestern Saudi Arabia is a mountainous area (altitude 3000 m) and is surrounded by the Tihama valley, where people live in close proximity to sheep, goats and dogs. In the last 4 years we have seen 108 patients with hydatid cysts of various organs; 6 of these patients had urinary tract involvement (4 had renal hydatids). This incidence is greater than that reported elsewhere (Halim and Vaezzadeh, 1980; Karabekios *et al.*, 1989) and it prompted us to review hydatids of the urinary tract treated in Asir Region Hospitals and to evaluate the various diagnostic tests in order to formulate a practical algorithm. We have also attempted to differentiate between communicating and non-communicating renal hydatid cysts, since the treatment of these 2 conditions is different.

Patients and Methods

Since October 1986, 10 patients with hydatid disease of the urinary tract were treated in Asir Region Hospitals. The case records were reviewed and each patient's age, sex, nationality, mode of presentation, investigations and treatment were analysed. The investigations included urine analysis, eosinophil count, indirect haemagglutination test (IHA), US, intravenous urography (IVU), CT and retrograde pyelography. Eight patients with histological evidence of hydatid disease had the results of their investigations (eosinophil count, US and CT) compared with those of age-matched and sex-matched controls with benign simple renal cysts in order to evaluate the efficacy of these investigations in the diagnosis of hydatid disease. The control patients with simple renal cysts had undergone percutaneous cyst aspiration (6) or open surgery for parapelvic cysts (2). Hydatid disease was excluded in this group either by examination of the aspirated fluid or by surgery. The efficacy of

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these tests is described in terms of sensitivity, specificity and accuracy. The significance of patient distribution in the 2 groups was tested using Fisher's exact test (Steel and Torrie, 1980).

We classified the renal hydatid cysts as either communicating or non-communicating, according to the presence or absence of communication with the pelvicaliceal system. Hydatid cysts due to *Echinococcus granulosus* were described as unilocular, as compared with the multilocular cysts of *Eschinococcus multilocularis*. They were further described as either multivesicular or univesicular, according to the presence or absence of daughter cysts within the main cyst (Saidi, 1976).

Results

All patients were Saudi nationals living in rural settings. There were 7 males and 3 females. The mean age of the males was 43 years (range 21–60) and for the females it was 36.6 years (range 20–55). The mean age of the control group was 40 years (range 30–65). Urine analysis confirmed hydatid disease in 2 patients with communicating renal cysts. IHA was positive in 6 of 8 patients and was not available in the control group.

Eosinophilia and hydatid disease

The number of patients with raised (>4%) or normal (<4%) eosinophil count in both groups was not significantly different ($P > 0.05$) (Table 1).

US and hydatid disease

Mixed echogenicity on US was compared in the 2 groups. All 4 patients with this feature were in the hydatid group. Of 12 patients without this feature, 4 were in the hydatid and 8 in the control group. The distribution of patients in the hydatid and control groups was significant ($P < 0.05$).

Table 1 Eosinophilia and Renal Cysts

	Renal cysts		
Eosinophilia	*Hydatid*	*Simple*	*Total*
>4%	4 (67%)	2 (33%)	6
<4%	4 (40%)	6 (60%)	10
Total	8	8	16

Sensitivity = 50%. Specificity = 75%. Accuracy = 62.5%. $P = 0.245$.

Table 2 Ultrasonography and Renal Cysts

US (Mixed echogenicity)	*Renal cysts*		
	Hydatid	*Simple*	*Total*
Positive	4 (100%)	0 (0%)	4
Negative	4 (33%)	8 (67%)	12
Total	8	8	16

Sensitivity = 50%. Specificity = 100%. Accuracy = 75%. $P = 0.039$.

CT and hydatid disease

The presence of a multivesicular cyst with mixed density on CT (Fig. 1) was compared in the 2 groups. All 7 patients with this feature were in the hydatid group (Table 3). In 9 patients without this feature, 1 was in the hydatid group and 8 were in the control group, The distribution of patients in the hydatid and control groups was significant ($P < 0.05$).

IVU and retrograde pyelography

IVU was performed in 8 patients and showed a mass in all of them. Only 2 could be diagnosed as hydatids owing to the presence of curvilinear calcification. There were no differentiating features between communicating and non-communicating

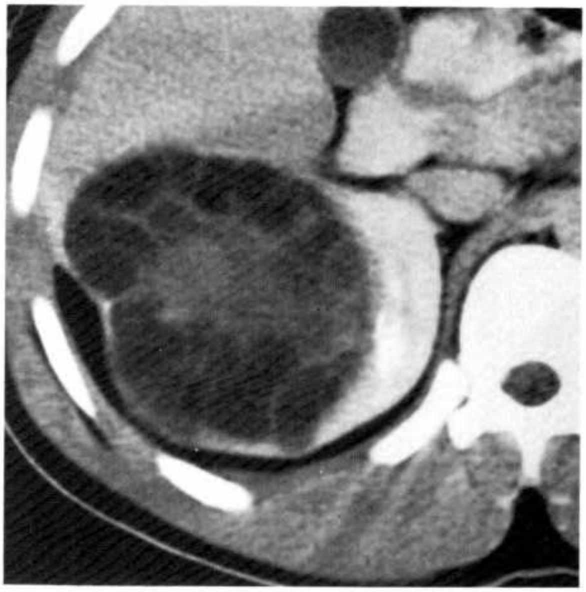

Fig. 1 CT scan showing multivesicular hydatid cyst of the right kidney with mixed density.

Table 3 CT Scan and Renal Cysts

CT (Multivesicular cysts and mixed density)	*Renal cysts*		
	Hydatid	*Simple*	*Total*
Positive	7 (100%)	0 (0%)	7
Negative	1 (11%)	8 (89%)	9
Total	8	8	16

Sensitivity = 87.5%. Specificity = 100%. Accuracy = 94%. $P = 0.006$.

renal hyatids. Retrograde pyelography was performed in 2 patients with communicating renal hydatid cysts and revealed distortion of the pelvicaliceal system with filling defects within the calices due to the daughter cysts (Fig. 2). However, the cyst cavity was not delineated by retrograde pyelography.

Discussion

The cestode *E. granulosus* resides in the intestine of dogs, the definitive host. The ova in the faeces of the dogs contaminate grass and farmland and are ingested by sheep, pig, goats or man—the intermediate host. After hatching, the larvae penetrate the duodenal wall and are carried to the liver by the portal stream. Those that escape the liver and lungs are disseminated by the arterial stream.

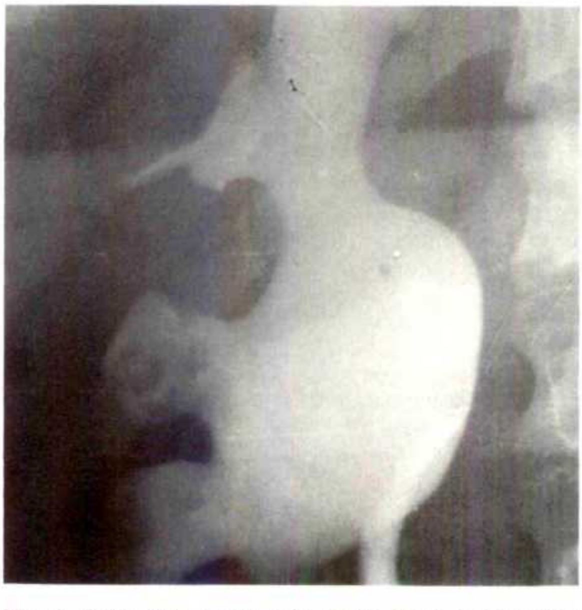

Fig. 2 Retrograde ureteropyelography showing intrapelvic filling defect in a communicating renal hydatid cyst.

Echinococcal involvement of the urinary tract is rare and renal hydatid cysts are said to comprise 2% of all hydatids (Halim and Vaezzadeh, 1980; Gilsanz *et al.*, 1980; Karabekios *et al.*, 1989). Within the urinary tract, the kidneys are the most commonly affected organs but hydatid cysts of bladder, prostate, seminal vesicles and testis are also reported (Selli *et al.*, 1983; Bahlman *et al.*, 1986; Kumar and Jahanshahi, 1987). The exclusively Saudi population reflects the prolonged contact between the host and the parasite. Both sexes are at risk because of the rural way of life in the Tihama valley and the mountainous terrain. Clinical features are not diagnostic of hydatid disease, being mainly abdominal masses and pain without urinary symptoms, except in the case of communicating renal hydatid cysts (Matos Ferreira and Rommel Rangel, 1979; Halim and Vaezzadeh, 1980; Al-Ani and Al-Waili, 1986). In 2 of our patients with communicating hydatids, the diagnosis was confirmed by examination of the hydatid membrane in the urine. The poor efficacy of eosinophilia is due to the high incidence of false positives in an area endemic with other parasitic infestations (Saidi, 1976; Halim and Vaezzedeh, 1980). Nevertheless, when eosinophilia is found in a patient with cysts in relation to the urinary tract, investigations should begin in order to rule out hydatid disease. Although IHA was raised in 6 of 8 patients in this study, it has a high incidence of false negatives owing to the circulating immune complexes and must be combined with tests for both antigen and antibody (Craig *et al.*, 1986). IHA also shows cross-reactivity with other parasitic infections such as cysticercosis and schistosomiasis (Rickard and Lightowlers, 1986). Among the radiological investigations, CT was more sensitive and accurate than US. Whilst US has a high sensitivity in hydatid disease of solid organs such as the liver (Beggs, 1983), its efficacy is reduced in urinary tract hydatids, with the cysts often being mistaken for simple renal cysts, hydronephrosis and ovarian cysts. CT was diagnostic of hydatid disease in 7 of 8 patients and showed multivesicular cysts with mixed density due to the daughter cysts (Kalovidouris *et al.*, 1986; Karabekios *et al.*, 1989). As in hydatids of the liver, the density of the daughter cysts was less than than of the mother cysts (Kalovidouris *et al.*, 1986). CT also measures the thickness of the residual renal parenchyma and the presence of intrapelvic cysts, in addition to the exclusion of cysts in relation to other organs. Occasionally, it may be impossible to differentiate between a univesicular hydatid and a thickened

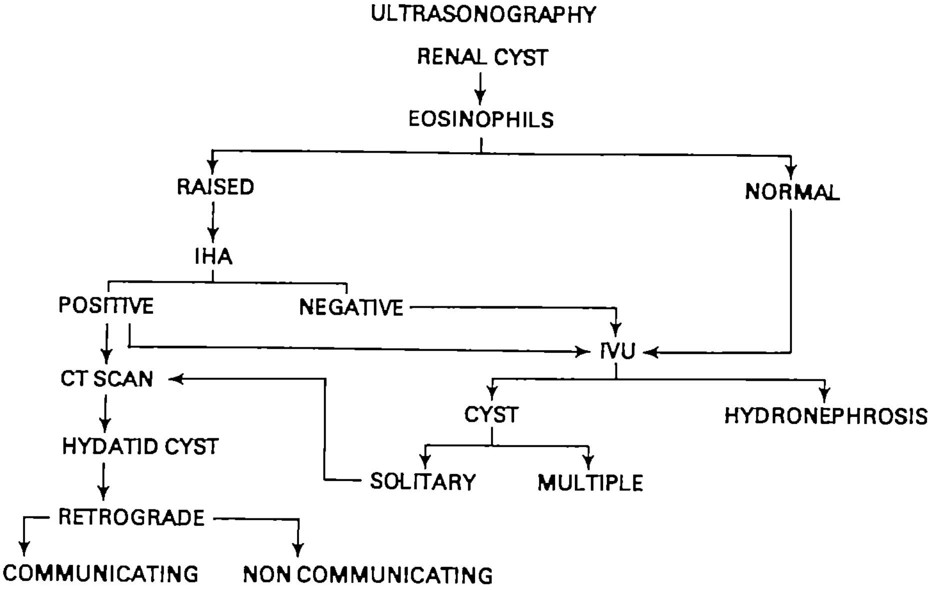

Fig. 3 Algorithm for investigation of a suspected urinary tract hydatid cyst

calcified benign infected cyst on CT, since both might show calcification of the wall (Karabekios *et al.*, 1989). The features on urography are due to the mass effect and show distortion of the pelvicaliceal system (Hertz *et al.*, 1984). Gilsanz *et al.* (1980) reported intrapelvic filling defects and opacification of the hydatid cyst by the contrast medium in communicating hydatids on IVU. We did not see this feature on IVU, probably because of the obstruction of the communicating tract by the daughter cysts. However, a retrograde study may be able to delineate the renal pelvis more clearly and not only demonstrate the filling defects but also show the communication of the cyst by displacing the obstructing daughter cyst by the force of the contrast injection. This retrograde study is useful in confirming communicating hydatids which might require nephrectomy, of which the patients can be forewarned, whereas in non-communicating cysts renal-sparing surgery can be performed. Renal angiography and isotope renal scans have been used in the past (Halim and Vaezzadeh, 1980; Al-Ani and Al-Waili, 1986) and have been now replaced by CT.

An algoritm is suggested for the diagnosis of urinary tract hydatid disease (Fig. 3). On detection of a renal cyst by US, an eosinophil count should be performed, followed by IHA in patients with eosinophilia. A subsequent IVU and CT, in selected cases, should diagnose most urinary tract hydatids. It is concluded that CT is the most diagnostic of all radiological investigations in urinary tract hydatid disease, and retrograde pyelography should be the investigation of choice to confirm a communicating renal hydatid cyst.

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Prognostic Value of Renal Venous Involvement in Renal Carcinoma

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Summary—A series of 108 renal tumour nephrectomies carried out between 1975 and 1984 was studied to determine the prognostic statistical significance of the relationship between venous involvement and various pathological features. Tumour size, spread, histological grade and lymph node involvement were compared between V0 tumours (58%), V1 (32%) and V2 tumours (10%). Actuarial 5-year survival rates revealed a poor prognosis with venous involvement (V0 66%, V1 27%, V2 33%). Tumours larger than 10 cm with perirenal spread and of higher histological grade were significantly related to venous involvement. Survival between renal vein involvement and inferior vena caval extension was statistically similar, but it was influenced by tumour size and higher grade. Perirenal spread and nodal involvement were poor indicators.

The prognostic significance of venous involvement in renal carcinoma is controversial. According to Robson *et al.* (1969), renal vein involvement adversely influences prognosis and therefore its presence is a criterion of stage 3 in their staging system. Other studies have supported (Sogani *et al.*, 1983; Theil *et al.*, 1985) or contradicted (Skinner *et al.*, 1971; Libertino *et al.*, 1987) the concept that renal vein involvement by itself is an adverse prognostic sign.

We studied 108 patients with renal carcinoma in order to assess the results of surgery with or without venous involvement and to determine other pathological features which influence the outcome of surgery.

Material and Methods

Complete records of 108 tumour nephrectomies carried out at St Vincent's Hospital, Dublin, between 1975 and 1984 were available. Detailed clinical presentation, physical signs and diagnostic investigations were recorded. Only cases of caval involvement where embolectomy was successful were included in this study. Complete information was available in 108 patients with a minimum follow-up of 5 years.

Detailed pathological information on the tumour specimen was obtained. The classification of tumour size was determined by the Petkovic (1975) methods. Size was divided into 3 categories: <5 cm, 5–10 cm, >10 cm. Tumour spread was divided into 3 groups:

1. Intrarenal tumour.
2. Histological infiltration of capsule or pelvis.
3. Infiltration of perirenal fat.

The histological grade of the tumour was classified according to the Erlangen-Nürnberg Group (Hermanek *et al.*, 1976). Grade 1: tumours include renal carcinomas which are exclusively of solid pattern and consist solely of so-called clear cells. Included are adenomas and doubtful malignancy. Grade 3: (a) tumours exclusively of glandular or glandular-papillary pattern; (b) tumours containing in at least one low power field (×64) exclusively dark (granular) cells, or (c) tumours with sarcoma-like areas. Grade 2: tumours which can neither be grouped grade 1 nor grade 3.

To study the prognostic significance of venous involvement, the V classification (UICC, 1974) was used. In this classification V0 designates veins not

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containing tumour, V1 renal venous system containing tumour and V2 denotes vena cava containing tumour.

Lymph node involvement was assessed for metastasis by histological examination of the nodes surrounding the renal pedicle removed with the kidney and also enlarged nodes which were removed during nephrectomy. As a policy, no formal retroperitoneal lymphadenectomy was carried out.

The relationship between the extent of venous involvement and pathological features—size, spread, histological grade and lymph node involvement—was studied by Kendall TAU-B rank correlation (Siegal, 1956). Actuarial survival curves were calculated by the method of Kaplan and Meier (1958). Differences in survival associated with venous involvement were analysed using the Log rank test (Peto *et al.*, 1977). A proportional hazard general linear model was used to calculate relative risk adjusted for confounding variables, using the SAS SUGI procedure PROC PHGLU (SAS Institute Inc., 1986), which includes a test for the proportional hazards assumption.

Results

Among the 108 tumour nephrectomies, 93 were carried out by the subcostal and 4 by the abdominal approach. Of the remaining 11 patients with inferior caval tumour, 9 had a thoraco-abdominal and 2 a lumbar nephrectomy; 67 were male and 41 female, with a ratio of 1.6:1. The age range was from 38 to 80 years (mean 63.1); 51 tumours were on the right side, 56 on the left and 1 bilateral.

Haematuria, weight loss and malaise were the most common presentations (Table 1). In 35% of patients the renal mass was palpable. Only 6% had varicoceles. Secondaries were present in 8% of cases. Hypertension and polycythaemia were present in 11 and 6% respectively. Pre-operative investigations included blood count, serum biochemistry, chest X-ray, ultrasonography and intravenous urography. When necessary, renal angiography and venography were carried out. Ultrasonography was the diagnostic investigation in relation to the size and venous extension of the tumour. Fifteen patients required venography for further assessment of vena caval thrombus. The commonest cause of false positive venous thrombus by ultrasonography was external compression and distortion of the vena cava by a medially placed renal tumour mass; 35% of patients underwent angiography and in 6% the renal artery was embolised.

Table 1 Clinical Presentation

		(%)
Haematuria	63	58
Pain	30	28
Mass	20	19
Triad	6	5
Malaise	38	35
Weight loss	43	40
Pyrexia	2	1.8
Miscellaneous		
Hepatomegaly	2	
Deep venous thrombosis	1	
Secondaries		
Bony (2)		
Lungs (7)	9	8.3
Palpable mass	38	35
Varicocele	7	6
Hypertension	12	11
Haemoglobin	< 10 gm% = 21	19
	> 17 gm% = 6	5

Table 2 Relationship of Tumour Diameter to Extent of Venous Extension

	< 5 cm (%)	*5–10 cm (%)*	*> 10 cm (%)*
None (V0)	13 (21)	37 (59)	13 (21)
Renal (V1)	1 (3)	17 (50)	16 (47)
Vena cava (V2)	3 (27)	8 (73)	

TAU = 0.305, $P < 0.001$.

Frequency of venous involvement

Thirty-four patients (32%) had tumour in the venous system; it extended into the inferior vena cava in 11 patients (10%) and 63 (58%) were free.

Relationship of tumour diameter and venous extension

In 13 patients (93%) with tumours less than 5 cm, veins were free of tumour. However, in 8 patients (73%) with inferior vena cava involvement the tumour exceeded 10 cm ($P < 0.001$) (Table 2).

Relationship of tumour spread and venous extension

In 29 patients (91%) with tumour confined to the paraenchyma, veins were free, while in 8 patients (73%) with vena cava involvement the tumour infiltrated the perirenal fat ($P < 0.001$) (Table 3).

Table 3 Relationship of Tumour Spread to Extent of Venous Extension

	Confined to parenchyma (%)	*Capsule/renal pelvis infiltration (%)*	*Fat infiltration (%)*
None (V0)	29 (46)	17 (27)	17 (27)
Renal (V1)	2 (6)	12 (35)	20 (59)
Vena cava (V2)	1 (9)	2 (18)	8 (73)

TAU = 0.410, $P<0.001$.

Relationship of histological grade and venous extension

In 39 grade I tumours (75%) the veins were free, but in 7 patients (64%) with inferior vena cava involvement the tumour was grade 3 ($P<0.001$) (Table 4).

Relationship between lymph node metastasis and venous extension

In only 52 patients was lymph node biopsy available. Since this was carried out only in the enlarged glands, data were biased by selection ($P=0.261$). In venous extension, however, 5 nodes (71%) were positive compared with 8 V0 cases (23%) (Table 5).

Survival

Actuarial 5-year survival rates in V0, V1 and V2 groups were 66%, 27% and 33% respectively; this was statistically significant between venous and non-venous involvement ($P<0.001$) (Fig.).

Table 4 Relationship of Histological Grade and Venous Extension

	Grade I (%)	*Grade II (%)*	*Grade III (%)*
None (V0)	39 (62)	14 (22)	10 (16)
Renal (V1)	11 (32)	13 (38)	10 (29)
Vena cava (V2)	2 (18)	2 (18)	7 (64)

TAU = 0.350, $P<0.001$.

Table 5 Relationship of Lymph Node Metastasis and Venous Extension (n = 52)

	Investigated	*Negative (%)*	*Positive (%)*
None (V0)	34	26 (76)	8 (23)
Renal (V1)	11	6 (55)	5 (45)
Vena cava (V2)	7	5 (71)	2 (29)

TAU = 0.150, $P=0.261$ not significant.

Eleven patients (10%) underwent vena caval embolectomy. Four patients required partial excision of the caval wall. One patient died 2 h postoperatively as a result of tumour thrombus in the right atrium. Of 3 patients who had associated pulmonary metastasis, 2 died at 6 months and 1 survived 20 months following excision of a pulmonary secondary. Two patients with lymph node metastasis survived 10 and 14 months.

Relative risks

For V0 R risk was 0.57 (CI 0.30–1.08) but V2 R risk was 1.46 (0.060–3.5).

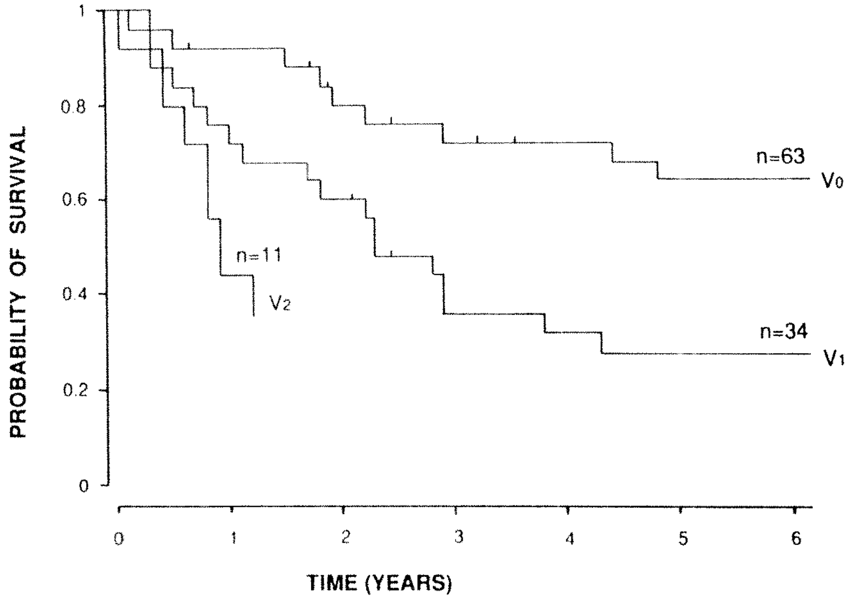
Prognostic factors

In patients with V0 tumours, poor prognostic factors identified by proportional hazards modelling were higher grade ($P=0.01$), older age ($P=0.008$) and larger tumour ($P=0.01$); spread was not significant ($P=0.84$).

In patients with V1 + 2 tumours, grade ($P=0.03$), size ($P=0.04$) and spread ($P=0.06$) were significant but age ($P=0.3$) was not.

Discussion

Renal carcinoma is well known for its tendency to invade the renal venous system and the reported incidence ranges from 11 to 62% (Robson *et al.*, 1969; Petkovic, 1975; Hoehn and Hermanek, 1983). In our experience, the incidence was 32%. Criteria have been variable, ranging from microscopic presence of tumour in the venous system to embolus with or without wall infiltration. Hoehn and Hermanek (1983) reported macroscopic renal invasion when divided according to tumour progression into branches, trunk of the renal vein or vena cava. There was no statistical difference in their 5-year survival rates; branches 28.8 ± 13.2%, trunk 35.7 ± 11.7% and inferior vena cava 42.6 ± 31.1%. However, prognosis was better where there was only microscopic evidence of venous involvement. Our experience has been a 27% 5-year survival rate with tumour present in branches and main trunk of



No. of patients at risk at corresponding times

Vo = 63	55	48	44	35	24	11
V1 = 34	24	20	12	9	6	3
V2 = 11	5	3	2	1	1	

Fig. Actuarial disease-free survival for V0, V1 and V2 tumours

renal veins suggestive of adverse effect by venous involvement. This supports the classification of venous involvement as a criterion of stage 3 disease (Robson *et al.*, 1969).

Since Skinner *et al.* (1971) reported a 55% 5-year survival rate in 11 patients after vena caval thrombectomy, other authors (Sogani *et al.*, 1983; Sossa *et al.*, 1984) reported that up to 50% of patients were disease-free at 20 months. In our experience with 11 patients, only 36% were still alive at 5 years; however, there was no statistically significant difference between V1 and V2 findings, as also reported by Hoehn and Hermanek (1983).

Age. There was no prognostic influence of age in the presence of venous involvement, a finding similar to that of Hermanek *et al.* (1976).

Size of tumour. An inverse relation between size of tumour and survival is well documented (Golimbu *et al.*, 1986; Medeiros *et al.*, 1988; Reis and Faria, 1988). Their data showed that tumour size was a prognostic indicator in the presence of venous involvement; 65% of tumours exceeding 10 cm had venous extension and this was related to poor prognosis.

Tumour spread

Kaufman and Mims (1966) and Kay (1968) reported that only 25 to 30% of patients with tumour invading Gerota's fascia survived for 5 years, as opposed to 63% without perirenal extension.

Skinner *et al.* (1971) and Golimbu *et al.* (1986) reported that invasion into perirenal fat rather than penetration of vein was significant. In our experience, the relation of venous extension to perirenal infiltration by tumour was significant ($P<0.001$) for survival. However, in V0 patients, spread into perirenal tissue was not a significant predictor.

Histological pattern

Several histological patterns of tumour have been described and their correlation with prognosis. Murphy and Mostofi (1965) noted that patients with granular cell tumours had a far worse prognosis than those with clear cell tumours. On the other hand, Lieber *et al.* (1981) found no difference but reported a worse prognosis for patients with spindle/anaplastic tumours. Fuhrman *et al.* (1982) studied nuclear grades 1 to 4 and their relation with prognosis, especially in stage 1 disease. They found that clear cell tumours were less aggressive than granular cell tumours. In nuclear grades 3 and 4, granular cell tumours accounted for 57% of cases. Medeiros *et al.* (1988) reported that renal vein invasion adversely affected prognosis only in high grade carcinoma. Papillary and spindle carcinomas independent of nuclear grade were associated with a significant decrease in survival compared with tumours with a solid pattern. In the present study, venous involvement was significantly correlated with grade 3 of the Erlagen-Nürnberg classification, *i.e.* the sarcomatoid anaplastic and tumour with granular cells, and this was related to poor survival.

Lymph node involvement

In the present series, 61% of lymph nodes were non-metastatic in V1 and V2 tumours, which is in agreement with the 64% reported by Studer *et al.* (1990). However, the relationship of nodal involvement between V0 and V1 and V2 tumours was not statistically significant. Studer *et al.* (1990) reported that 58% of enlarged nodes revealed inflammatory changes and/or follicular hyperplasia more frequently in patients with renal vein involvement. In our experience, selective negative nodal biopsy of enlarged nodes did not show any improved survival with venous involvement.

It was concluded that tumour penetration into veins is a biological characteristic of renal carcinoma. The incidence in the present series was 42% and was related to poor prognosis. Five-year survival was statistically significant between V0 and V1 and V2 tumours.

Survival rates in patients with involvement of the renal vein and the inferior vena cava were found to be statistically similar, but this was influenced by tumour size and histological grade. Perirenal spread and nodal involvement were poor indicators.

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Long-term Results of Surgical Treatment of Renal Carcinoma in Solitary Kidneys by Extracorporeal Resection and Autotransplantation

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Summary—We describe the technique and present the long-term results of extracorporeal partial nephrectomy and autotransplantation in 6 patients with renal carcinoma. During a follow-up period exceeding 5 years, dialysis was not required and the patients' blood pressure improved or remained within normal limits. One patient died post-operatively from gastrointestinal bleeding. The mean duration of follow-up was 54 months (range 14–97). The alternatives to extracorporeal resection and autotransplantation (such as complete nephrectomy and *in situ* resection of the tumour) are discussed.

Renal carcinoma accounts for 80 to 90% of all primary malignancies of the kidney (Deming and Harvard, 1970; Skeet, 1976; Richie and Skinner, 1981; Paulson *et al.*, 1985). In the USA, the incidence is 7.5/100,000 and the disease accounts for 2.1% of male and 1.6% of female deaths (Richie and Skinner, 1981). Patients can be cured by radical nephrectomy, which generates few problems if the other kidney is present and functions satisfactorily. However, if the tumour occurs in a solitary kidney or in the only functioning kidney, nephrectomy results in complete loss of renal function and dialysis is inevitable. Although the tumour can be locally resected, thus preventing complete loss of kidney function, several disadvantages are associated with this technique. Firstly, partial resection may result in inadequate resection of the tumour and, secondly, the remaining part of the kidney may be damaged both by the surgical procedure and by ischaemia, resulting in inadequate renal function and dialysis. In an attempt to solve this problem we have performed extracorporeal resection and autotransplantation. This procedure includes nephrectomy, preservation of the kidney and subsequent autotransplantation of the remaining part of the kidney (Terpstra *et al.*, 1981). It also provides optimal protection of all remaining renal tissue and complete resection of the tumour. We describe the technique and present the long-term results in a selected group of patients with renal carcinoma in a solitary functioning kidney.

Patients and Methods

From 1979 to 1987, 6 patients with renal carcinoma underwent extracorporeal resection and autotransplantation at the University Hospital Leiden. The 3 men and 3 women ranged in age from 47 to 72 years (mean 63.5). Five patients had a solitary kidney following nephrectomy because of calculi, tuberculosis, renal carcinoma (1 patient each) or because of end-stage pyelonephritis (2 patients). In the sixth patient (Case 6) both kidneys were present but did not function adequately and in this patient the primary indication for surgery was renovascular hypertension and insufficiency. The tumour was an accidental finding on pre-operative ultrasound examinations which had been performed to measure the length of the kidneys. The diagnosis of carcinoma was made after histological examination

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of the tumour, which was removed during extracorporeal reconstruction and autotransplantation.

Pre-operative investigations included liver function tests (SGPT, SGOT, LDH) and assessment of renal function (serum creatinine, blood urea nitrogen). In the 5 patients with a solitary kidney the pre-operative creatinine levels varied between 88 and 173 µmol/l (mean 120.4). In the sixth patient, who also had renovascular hypertension, the creatinine level was 989 µmol/l on dialysis owing to bilateral renal artery occlusion. In the 5 patients with a solitary kidney the pre-operative systolic blood pressure ranged between 114 and 160 mmHg (mean 141.6) and the diastolic between 75 and 97 mmHg (mean 87.2). The patient with renovascular hypertension had a blood pressure of 225/130 mmHg.

Staging of the tumour was done by means of chest X-ray, bone scan, CT scan and arteriography. Patients were selected for surgical treatment only if there was no evidence of metastases. The tumours were classified according to the TNM system of the International Union against Cancer (UICC) (Hermanek and Sobin, 1987). The pre-operative classification of the tumours was T2 (4 cases) and T3 (2 cases). Postoperative histopathological grading was done according to the cell type, degree of uniformity in size and staining of the cells. Blood vessel infiltration and the presence of tumour cells in the resection margins was documented.

The surgical procedure consisted of nephrectomy, workbench surgery and autotransplantation (Terpstra *et al.*, 1981). After intravenous administration of mannitol, nephrectomy was performed. The ureter was not transected. Subsequently the kidney was perfused continuously with Euro-Collins solution at 4°C and placed on melting ice slush in a flat basin on top of the patient's pubic bone. The ureter was clamped with a tourniquet during workbench surgery. The tumour was resected with margins of at least 1 cm. In 3 of the 6 cases frozen sections were examined to establish whether the tumour had been completely removed. Continuous perfusion with Collins solution allowed identification of leaking vessels, which were repaired with 7/0 Prolene® sutures. Meticulous restoration of the urinary collecting system followed and the transected parenchyma was covered with renal capsule or a free peritoneal patch. Subsequently, autotransplantation to the iliac vessels was performed using standard renal transplant techniques.

All patients were followed up at regular intervals in the out-patient clinic. Observations included history, physical examination (including blood pressure), evaluation of renal function and the possible presence of metastatic growth. The duration of follow-up varied between 26 days and 97 months (mean 54 months). No patient was lost to follow-up. Details of each patient's progress are given in the Table.

Results

The duration of warm ischaemia, which was required for performing the arterial and venous anastomoses during autotransplantation, ranged from 20 to 31 min (mean 26.9). Cold ischaemia during resection and workbench repair ranged from 45 to 221 min (mean 156). The patient who was on dialysis before operation underwent simultaneous reconstruction of the left renal artery with a venous bypass together with resection of the stenosis in the right renal artery and autotransplantation after local resection of the tumour. Her serum creatinine returned to normal within a few days.

Post-operatively none of the patients required dialysis. In all cases radical macroscopic resection was possible. Five patients had a single tumour, varying in size from 1 to 10 cm. In the remaining patient 2 tumours were removed (measuring 4 and 8 cm). During surgery the frozen sections of the margins in 3 cases showed no residual tumour cells. In all cases permanent sections of the tumour and the resection area were taken. Clear cell tumours were found in 4 patients, basophilic in 1 and chromophobic in the other. Vascular invasion was found in the final sections in 2 patients (cases 1 and 5). Paraffin sections of the resected areas were free of tumour in 5 cases. In Case 5 the pathologist could give no firm opinion on the completeness of tumour removal because the histopathological sections were inadequate. The mean duration of follow-up was 54 months, with 3 patients being followed up for more than 5 years. Three patients died during follow-up and in 2 cases autopsy was performed. In Case 3, who died from gastrointestinal haemorrhage 26 days after the operation, 6 metastases were found in the thyroid gland. In Case 5, who died from pneumonia 17 months postoperatively, residual tumour was found with metastases in the inferior vena cava at the site of the former right renal vein. Case 1 died from liver cirrhosis with no clinical evidence of recurrent tumour; autopsy was not performed.

Blood pressure levels decreased or remained the same as those recorded preoperatively in all patients (systolic 110–170 mmHg (mean 140.2), diastolic

Table Details of Patients

Case no	*Age (years) and sex*	*Status of contralateral kidney*	*Staging*	*No of tumours*	*Size (cm)*	*Histology*	*Warm ischaemic time (min)*	*Cold ischaemic time (min)*	*Pre-operative creatinine (µmol/l)*	*Post-operative creatinine (µmol/l)*	*Pre-operative blood pressure (mmHg)*	*Post-operative blood pressure (mmHg)*	*Follow-up (months)*	*Status of patient at last follow-up*
1	64 M	L nephrectomy (stones)	T3 NO MO	1	8	Clear cell, grade 3, vaso-invasive	25	221	113	111	135/85	110/75	70	Died from liver cirrhosis
2	47 F	R end-stage pyelonephritis	T2 NO MO	1	3.5	Clear cell, grade 2, not vaso-invasive	28	130	89	100	150/93	135/81	97	Alive
3	67 M	Bilateral tumour L nephrectomy previously performed	T2-3 NO MO	2	8/4	Clear cell, grade 2, not vaso-invasive	27	152	173	501	160/97	170/85	26 days	Died from GI bleeding. Autopsy showed 6 metastates in thyroid gland
4	72 M	R end-stage pyelonephritis	T2 NO MO	1	8	Chromophobic, grade 2, not vaso-invasive	28	210	139	164	149/86	170/80	72	Alive
5	64 F	L nephrectomy due to tuberculosis	T3 NO MO	1	10	Basophilic, grade 3, vaso-invasive	31	114	88	111	114/75	115/75	17	Died from pneumonia, invasive growth in vena cava
6	67 F	Bilateral nephrosclerosis	T2 NO MO	1	6 5	Clear cell, grade 2, not vaso-invasive	20	45	989 (on dialysis)	124	225/130	153/81	14	Alive

75–90 mmHg (mean 81.0)). Serum creatinine levels remained within the normal range in 5 patients. In Case 3 the creatinine level increased from 173 μmol/l pre-operatively to 501 μmol/l before death 26 days after the operation. In Case 6, creatinine levels decreased from 989 μmol/l on dialysis before the operation to 124 μmol/l after the operation, at which time haemodialysis ceased. In this patient renal function improved not only following reconstruction of the right kidney with the tumour but also following reconstruction of the left renal artery, since isotope studies demonstrated that both kidneys were functioning adequately. Serum creatinine levels in the 6 patients ranged between 100 and 501 μmol/l (mean 172.6).

Discussion

This study demonstrates that nephrectomy, workbench surgery and autotransplantation can cure selected patients with renal carcinoma in a solitary functioning kidney. Alternatively, complete resection of the affected kidney can be performed, but haemodialysis would then be inevitable. Depriving a patient of all renal function by total nephrectomy can be followed by cadaveric renal transplantation, but this seems unattractive for several reasons. The waiting period on dialysis and the additional risks of cadaveric renal transplantation in patients who have had cancer may make this approach unsuitable for many patients (Zincke and Sen, 1988). Furthermore, the cost of haemodialysis and renal transplantation is very high (Zincke *et al.*, 1985).

Another alternative is *in situ* resection of the tumour, but this technique is more difficult when the tumour is large or occupies a central position in the kidney (Jacobs *et al.*, 1980; Lawson, 1980; Novick, 1982; Zincke and Sen, 1988). Thus technical difficulties may result in incomplete tumour resection or in irreversible damage to the residual kidney parenchyma. Although incomplete resection could also be a problem with the extracorporeal procedure, pathological verification of the completeness of tumour removal is easy and resection of residual tumour is simple when compared with "*in situ*" resection where enucleation of the tumour is often performed. Marshall *et al.* (1986) found that 6 of their 15 patients treated with simple enucleation had residual tumour cells in the margins of the resection. Jacobs *et al.* (1980) showed that local recurrence was probably less common in autotransplanted kidneys (1 of 17) than in those treated *in situ* (5/42). Zincke and Sen (1988) found only 1 local recurrence in 9 patients treated by extracorporeal resection. Novick *et al.* (1989) reported local tumour recurrence in 2 of 23 patients treated by enucleation of the tumour, in 8 of 86 who underwent *in situ* excision of the tumour and in only 1 of 14 patients who underwent *ex vivo* excision. With 1 recurrence at the site of the nephrectomy among 6 patients treated by extracorporeal excision we confirm the excellent results of these authors. The renal carcinoma metastases which were found in the thyroid gland of Case 3 at autopsy were not recognised before the operation and could not have been related to the technique of extracorporeal resection, since there was no local recurrence.

It is evident that extracorporeal excision of the tumour and autotransplantation is a more extensive operation than the alternatives mentioned above. It is also more time-consuming and is associated with more potential morbidity. However, the advantages include optimal exposure, a bloodless surgical field, the ability to perform a more precise operation with maximal preservation of renal parenchyma, greater protection of the kidney from prolonged ischaemia and less risk of tumour spillage (Lawson, 1980; Novick, 1982, 1987). The experience required for this more extensive procedure was available in our unit because the technique had been adapted from the extracorporeal renal artery reconstruction procedure which we use to repair distal branch lesions in patients with renovascular hypertension (Terpstra *et al.*, 1981; Van Bockel *et al.*, 1987, 1991). This experience helped to minimise complications such as urinary leakage, fistulas, ureteric obstruction or vascular problems. Zincke and Sen (1988) reported that of their 11 autotransplanted kidneys with renal carcinoma, graft nephrectomy had to be performed twice because of venous or arterial thrombosis and once because of ureteric and pelvic complications. Each of these complications was prevented in our small series.

Metastases, vascular or urological problems were not observed during long-term follow-up. The only exception was the patient with asymptomatic tumour invasion of the inferior vena cava noted at autopsy 17 months post-operatively (the cause of death being pneumonia).

Almost as important as radical resection of the tumour was the preservation of adequately functioning renal tissue. This was achieved relatively easily and was confirmed by the satisfactory serum creatinine levels, the absence of temporary or maintenance dialysis and normal blood pressure levels. Zincke and Sen (1988) also reported acceptable creatinine levels but Novick *et al.* (1989) observed initial non-function of the repaired kidney in 5 of 14 patients undergoing extracorporeal resection compared with only 2 of 86 patients undergoing an *in situ* procedure. In their study, renal failure occurred in 2 of 14 patients treated by extracorporeal resection and in only 1 of 86 repaired *in situ*. However, it should be noted that these 2 groups of patients were not completely comparable.

Long-term follow-up of this small series and the results which we obtained in patients with renovascular hypertension (Van Bockel *et al.*, 1987, 1991) lead us to believe that extracorporeal partial nephrectomy and autotransplantation is a safe and reliable technique which can be used to cure patients with a centrally located renal carcinoma in a solitary kidney. Alternatives such as partial nephrectomy *in situ* cannot always be used because of the risk of tumour recurrence and impaired renal function. In this respect extracorporeal resection is a useful alternative to radical nephrectomy, which inevitably leads to dialysis. Although there is the possibility of renal transplantation in the future, there is still no better donor than the recipient if one has to receive a kidney (Milsten *et al.*, 1974).

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Phase II Clinical Trial of Recombinant alpha-2 Interferon for Biopsy-proven Metastatic or Recurrent Renal Carcinoma

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Summary—Twenty patients with histologically confirmed metastatic or recurrent renal carcinoma were treated in a phase II study with alpha-interferon (2–5 × 10^6 U/m^2 subcutaneously, 3 times a week). Nineteen patients had multiple sites of disease and 18 had previously undergone nephrectomy; 9 had an ECOG performance status of 0·1, and 11 had a performance status of 2–3. There was one partial response, yielding an overall response rate of 5%. Treatment was well tolerated, although 7 patients developed influenza-like symptoms, and in 2 cases this was sufficiently severe for the patients to request cessation of treatment. As a single agent at this dose schedule, alpha-interferon has minimal activity in the treatment of renal carcinoma and cannot be recommended as standard therapy. The difference in outcome between this and some published series may reflect the stringent requirement for histological proof of the presence of metastases.

A relapse rate of more than 50% has been reported after surgical resection of renal carcinoma, and more than 50% of new patients have metastatic disease at first presentation (Harris, 1983; Muss, 1988).

There is no defined role for chemotherapy in these patients (Linehan *et al.*, 1989), although anecdotal clinical evidence has suggested that the natural history of renal carcinoma may be influenced by the natural defence mechanisms of the body (Harris, 1983; Muss, 1988; Quesada, 1988). Thus a number of treatment modalities have been used in an attempt to influence host defences, including bacillus Calmette-Guérin (BCG), interferons, anti-tumour monoclonal antibodies, interleukin-2 and lymphokine-activated killer cells (Harris, 1983; Rosenberg *et al.*, 1987; Muss, 1988; Quesada, 1988). More recently, therapies incorporating interferon and interleukin-II (Krigel *et al.*, 1990) and the combination of coumarin and cimetidine (Dexeus *et al.*, 1990) have been developed.

Recombinant alpha-2 interferon has been reported to produce response rates between 0 and 29% (Quesada, 1988). Many of these trials have involved very small numbers of patients and have been biased by the proportion of patients with good prognostic features (*i.e.* good performance status, lung metastases only or resection of the primary) (Muss, 1988; Quesada, 1988).

We have performed a standard phase II study with strict response criteria (Miller *et al.*, 1981) in patients with histologically confirmed metastatic or recurrent renal carcinoma in order to define the true level of activity of alpha-2 interferon.

Patients and Methods

Between April 1988 and August 1990, 20 patients with evaluable or measurable recurrent or metastatic renal carcinoma were studied. Biopsy confirmation of the presence of metastases was a

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prerequisite for treatment. Written informed consent was required.

Fourteen patients were male (median age 56 years, range 39–64). Two patients had a performance status (PS) of 0, 7 had PS 1, 10 had PS 2 and 1 had PS 3, assessed according to the criteria of the Eastern Cooperative Oncology Group (Oken *et al.*, 1982). Characteristics of the patients are summarised in Table 1.

Nephrectomy had been performed in 18 patients and 8 had received prior systemic treatment. This included 6 patients who had received a progestational hormonal agent and 2 who had been treated with vinblastine. In addition, 4 patients had received localised palliative radiotherapy prior to enrolment. Eight patients had received no therapy prior to the commencement of interferon, 14 presented with recurrent disease following nephrectomy and 6 had metastatic disease at the time of the original diagnosis. The sites of disease are shown in Table 2. Eighteen patients had more than one site of metastatic disease.

Patients previously treated with immunological therapy or radiotherapy to the sole index lesion were not eligible. Similarly, those who had received chemotherapy within the preceding 3 weeks, or those who had received more than one protocol of chemotherapy, were not eligible. Other exclusion criteria included patients with an ECOG performance status of 4, a history of other malignancy, or intercurrent life-threatening illness.

Table 1 Details of Patients

	No. of patients
Age (years)	
Median 56	
(range 39–64)	
Sex	
Male	14
Female	6
ECOG	
0	2
I	7
II	10
III	1
Primary resected	
Yes	18
No	2
Disease status	
Recurrent	14
Metastatic (at presentation)	6
Previous treatment	
Progesterone	6
Vinblastine	2
Local radiotherapy	4
Nil	8
Maximum dose of interferon (U/m^2)	
2×10^6	2
3×10^6	6
4.5×10^6	2
5×10^6	10

Table 2 Sites of Disease

	No. of patients
Liver	11
Bone	10
Lymph node	9
Lung	9
Renal bed	6
Abdominal nodes	5
Adrenal	1
Contralateral kidney	1
Spleen	1

Recombinant alpha-2 interferon (Schering-Plough Pharmaceuticals, Sydney) was given subcutaneously 3 times a week at an initial dose of 2×10^6 U/m^2. As significant toxicity was not observed at this dose in the first 4 patients, the initial dose was increased to 3×10^6 U/m^2, with a further escalation to 5×10^6 U/m^2 after 2 weeks. Treatment was continued for 3 months unless there was objective evidence of tumour progression or unacceptable toxicity. Patients with unacceptable toxicity had the option of a serial dose reduction to a minimum of $1{\cdot}5 \times 10^6$ U/m^2 if required.

The maximum dose of interferon was 5×10^6 U/m^2 in 10 patients, 4.5×10^6 U/m^2 in 2, 3×10^6 U/m^2 in 6 and 2×10^6 U/m^2 in 2. Interferon was continued for a median of 10 weeks (range 1–45).

Patients were reviewed each month and response and toxicity were assessed according to standard criteria (Miller *et al.*, 1981). Patients were considered evaluable for response and toxicity following the commencement of treatment. Objective assessment of response was made after 3 months of therapy. Those who demonstrated progressive disease ceased treatment at the time of progression. Those with stable disease (Miller *et al.*, 1981) and persistent symptoms ceased therapy after 2 months. The protocol allowed those who achieved either a complete or partial response to continue treatment for a further 9 months or until progression of disease.

Results

One patient developed progressive disease 2 weeks after the commencement of interferon and 2 others developed progressive disease after 3 weeks. One patient developed rapidly progressive disease 7 days after the commencement of interferon and died 2 weeks later.

None of the 20 patients achieved a complete response and only 1 achieved a partial response (95% confidence intervals 0–14%). The site of objective response in this patient consisted of biopsy-proven multiple liver metastases. The time to achievement of the partial response was 14 weeks and the duration of response was 5 weeks. Treatment was stopped because of unacceptable lassitude and the patient subsequently developed progressive disease. When retreated with interferon he obtained a further partial response which was maintained for 13 weeks.

Seven patients had stable disease and 8 had progressive disease. Those with stable disease eventually progressed at a median of 10 weeks (range 2–16).

Currently 6 patients are alive and all have evidence of cancer. The median time to either death or last follow-up for all patients from the time of diagnosis was 20 months (range 5 weeks–16.7 years) and from the time of commencement of interferon was 15 weeks (range 3 weeks–20 months).

Toxicity encountered during the study is shown in Table 3. The major toxicity was an influenze-like syndrome characterised by myalgia, arthralgia, fever and severe lassitude. This occurred in 7 patients and was so severe in 2 that treatment was discontinued following an initial dose reduction.

Grade I anaemia occurred in 3 patients, grade II in 5 and grade III in 2. One patient developed Grade II leukopenia. There was no thrombocytopenia.

Other side effects were generally mild. Grade II nausea and vomiting occurred in 1 patient and 3 developed Grade I diarrhoea, stomatitis and rash respectively. There were no treatment-related deaths.

Table 3 Toxicity of Interferon (Worst Toxicity in 20 patients)

	No. of patients with toxicity according to WHO				
Grade	*0*	*1*	*2*	*3*	*4*
Hb	10	3	5	2	0
White cell count	19	0	1	0	0
Platelets	20	0	0	0	0
Nausea, vomiting	19	0	0	1	0
Diarrhoea	19	1	0	0	0
Rash	19	1	0	0	0
Stomatitis	19	1	0	0	0

Discussion

The response rates and survival benefits reported in clinical trials of biological response modifiers in renal carcinoma are varied. In the case of the interferons, response rates of 0 to 29% have been reported (Quesada, 1988). There are several reasons for this variation. Bias may result from the inclusion of patients with favourable prognostic features, such as good performance status, the presence of lung metastases without other sites of visceral involvement, and in cases where the primary tumour has been resected. Histological confirmation of metastatic or recurrent renal carcinoma is also an important factor, as some lesions seen in patients with renal carcinoma are due to coincidental conditions (Kirk, 1987). In addition, some responses to therapy may be due to the rare but well established phenomenon of spontaneous regression (Kirk, 1987). This phase II study applied strict criteria of evaluation to a group of patients with metastatic or recurrent renal carcinoma. The low response rate seen in these patients suggests that alpha-interferon in this setting has little activity. It should be noted that 18 patients received at least 3×10^6 U/m^2 and 10 received 5×10^6 U/m^2 thrice weekly, suggesting that the lack of response was not a dose-related phenomenon, as other studies have shown responses at these doses (Quesada, 1988). Furthermore, 18 patients had already undergone nephrectomy and none was heavily pretreated.

Although 7 patients had stable disease for a median of 10 weeks, this may have been a function of the natural history of the disease rather than the influence of alpha-2 interferon.

Seven patients developed the typical influenza-like syndrome, and this necessitated cessation of treatment in 2 instances. The treatment was otherwise well tolerated, although moderate (grade 2–3) anaemia (Miller *et al.*, 1981) was a frequent finding.

In conclusion, we have applied strict criteria of histological proof of metastases and rigorous indices for assessment of response in determining the efficacy of alpha-2 interferon in a heterogeneous group of patients with renal carcinoma. Despite treatment being well tolerated, alpha-interferon in the dose range of $2\text{–}5 \times 10^6$ U/m^2, administered thrice weekly, had minimal activity and cannot be considered as adequate single agent therapy for this disease.

Acknowledgements

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Endometriosis of the Ureter

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Summary—Five patients with ureteric endometriosis are described. Extensive pre-operative investigation failed to reveal the aetiology of the unilateral upper urinary tract obstruction seen in all of these patients. Due to the dense fibrosis that invariably accompanies ureteric endometriosis, early surgical excision of the ureteric stricture permits effective resolution of upper tract dilatation and improved renal salvage.

Ureteric obstruction produced by endometriosis was first reported by Cullen in 1917. By the early 1980s, approximately 100 cases had been reported (Williams, 1987). When endometriosis involves the urinary tract, the bladder is most commonly affected (84%), and the ureter is involved in only 15%. Symptoms are either non-specific or insidious in onset. Medical treatment such as danazol (an isoxazol derivative of 17α-ethanyltestosterone) (Rivlin *et al.*, 1985), oestrogens (Karnaky, 1955), medroxyprogesterone acetate (Andrews, 1980) and androgens have all been used with varying success, but medical treatment alone has rarely succeeded in improving the obstruction permanently.

Patients and Methods

Case 1. A 44-year-old lady presented with a history of left loin pain and difficulty in micturition. Bacteriuria was documented on urine microscopy. Intravenous urography demonstrated obstruction of the lower left ureter but no evidence of urolithiasis. Pre-operative ascending ureterography confirmed the level and degree of obstruction (Fig. 1) but was not diagnostic. At operation, the obstructed left ureteric segment was firmly adherent to a left tubo-ovarian mass and was excised. Ureteric continuity was restored by intubated uretero-ureterostomy. Histological examination of the resected specimen revealed extrinsic ureteric endometriosis and dense fibrosis. Two months later the patient was asymptomatic, her urine was sterile and acellular and intravenous urography confirmed free drainage of the left ureter.

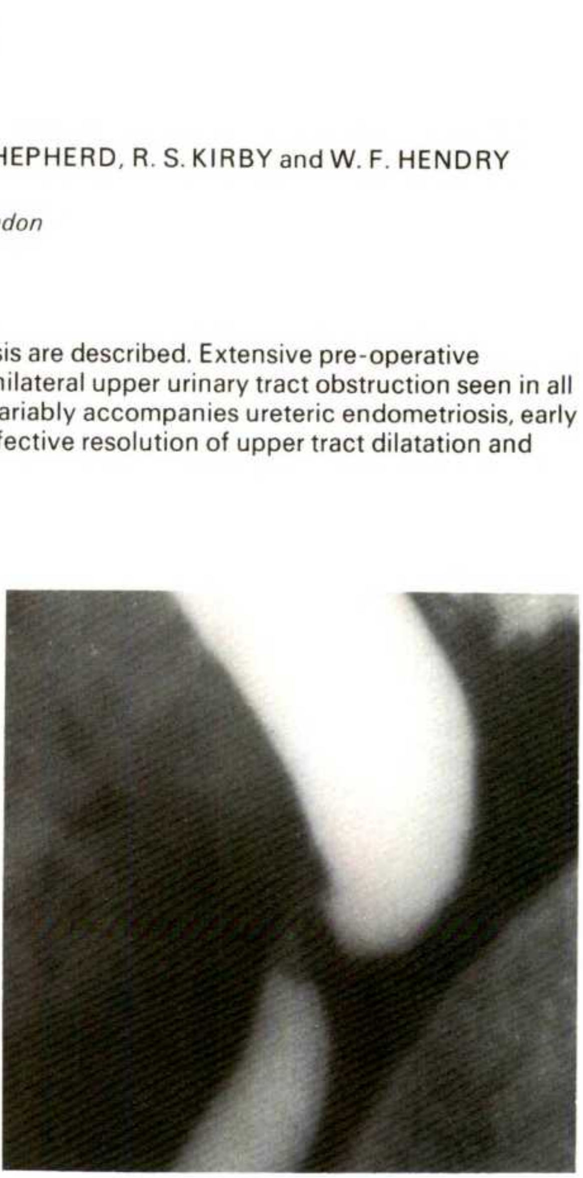

Fig. 1 Ascending left ureterogram demonstrating almost complete obstruction of the pelvic ureter.

Case 2. A 51-year-old lady presented with a 7-month history of cyclical left loin pain, not associated with menstruation. Serum and urine investigations were unremarkable. Intravenous urography demonstrated lower left ureteric obstruction of undetermined cause. Subsequent CT scan revealed small bilateral cystic areas within the pelvis and confirmed left ureteric obstruction adjacent to the cervix uteri. Ascending left ureterography demonstrated almost complete obstruction approximately 5 cm proximal to the vesicoureteric junction.

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A red polypoid swelling was seen at the level of obstruction by rigid ureteroscopy. Extraperitoneal excision of the ureteric stricture with intubated uretero-ureterostomy was performed. Histological examination revealed intrinsic ureteric endometriosis (Fig. 2). At 2 months the patient was asymptomatic, and both intravenous urography and isotope renography confirmed complete resolution of the obstruction.

Case 3. A 38-year-old lady presented with a 2-week history of urinary frequency, dysuria and intermittent left loin pain. Clinical examination suggested pyonephrosis. Urine microscopy revealed haematuria and sterile pyuria. Serology was unremarkable except for a leukocytosis. Percutaneous needle nephrostomy drainage was effected, and subsequent antegrade ureterography revealed complete ureteric obstruction of undetermined origin at the level of the ischial spine. Isotope renography demonstrated 25% left renal function. Contrast CT scan did not show a definite cause for the obstructed left pelvic ureter. At laparotomy, a short inflammatory stricture of the left ureter was excised with intubated uretero-ureterostomy reconstruction. Histology revealed extrinsic endometriosis and surrounding dense fibrosis. Three months later the patient remained well with almost complete resolution of upper tract dilatation on intravenous urography.

Case 4. A 32-year-old lady presented with lower abdominal discomfort. At laparotomy 7 years previously for left iliac fossa pain, a mass involving the pelvic colon was excised, a histological diagnosis of endometriosis was made and the patient was given a 1-year course of treatment with danazol. Six years later, at the age of 31, a hysterectomy was performed for menorrhagia and pelvic pain. At this admission, ultrasound revealed an 8-cm mass in the left side of the pelvis. Intravenous urography demonstrated left hydronephrosis and hydroureter with thinned renal parenchyma and indentation of the bladder by the extrinsic mass (Fig. 3A). At laparotomy, the extensive retroperitoneal mass, involving both tubes and ovaries, was resected *en bloc* with a 3-cm segment of the lower left ureter. Left ureteroneocystostomy was then performed. Histological examination again confirmed extrinsic ureteric endometriosis with dense fibrosis. Intravenous urography 2 months later revealed some resolution of the left upper tract dilatation, and the patient remained asymptomatic (Fig. 3B).

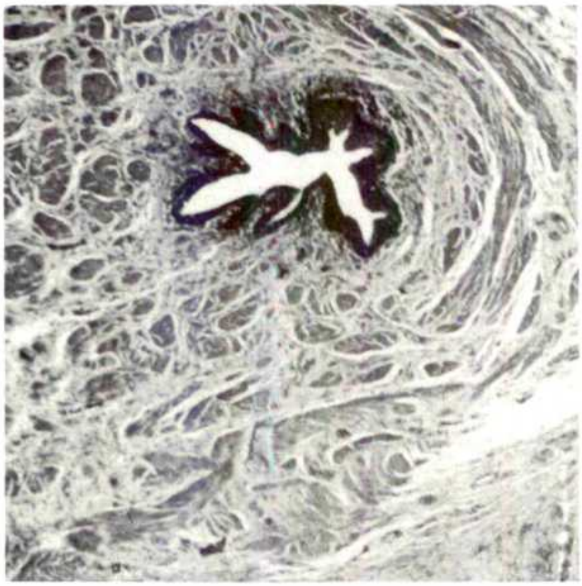

Fig. 2 Intrinsic ureteric endometriosis with surrounding dense fibrosis (× 15).

Case 5. A 40-year-old lady presented with low abdominal pain, dysuria, urinary frequency and intermittent vaginal bleeding 5 years after a hysterectomy and right oophorectomy. Serology was normal and urine microscopy revealed scanty red cells and sterile pyuria. Intravenous urography demonstrated a non-functioning right kidney which, on ultrasound, was hydronephrotic to the level of the vesicoureteric junction. This was confirmed by CT scan but no definite mass was visualised in the pelvis. At laparotomy, the lower right ureter was encased in an inflammatory mass posterior to the bladder and extending laterally around the apex of the vagina and the right side of the rectum. Right nephroureterectomy was performed. Histology showed diffuse cortical scarring and almost complete loss of the medulla. The lower ureter was surrounded by dense fibrous tissue containing foci of endometriosis. The patient was subsequently referred for regular gynaecological review and was commenced on a 2-year course of danazol.

Discussion

A series of 5 patients with ureteric endometriosis is reported. Three presented with loin pain and symptoms of "cystitis" and 2 presented with pelvic discomfort; 1 was found to have a pelvic mass. Intravenous urography demonstrated unilateral hydronephrosis and hydroureter with ureteric obstruction within the pelvis on the affected side. Ascending ureterography was performed in 3 patients and confirmed the level of the ureteric obstruction (Fig. 1). Pelvic ultrasound and CT scans were performed in 3 patients; cystic areas were seen in the pelvis in only 1 of these and the cause of the ureteric obstruction was not defined. A palpable pelvic mass was present in 3 patients. One patient (later found to have intrinsic ureteric endometriosis) underwent rigid ureteroscopy, at which a lower ureteric polypoid lesion was suspected.

All patients then underwent laparotomy. An

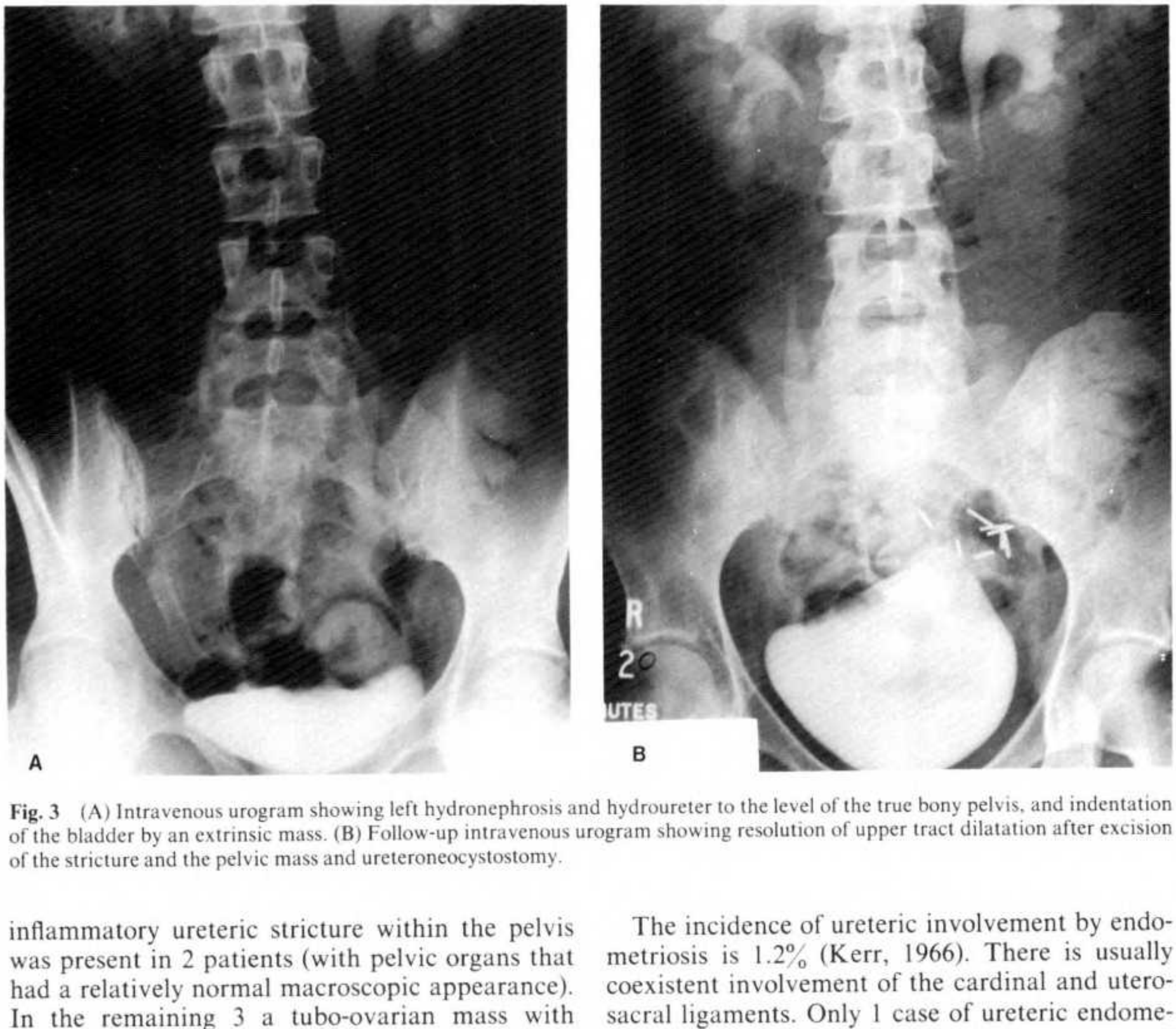

Fig. 3 (A) Intravenous urogram showing left hydronephrosis and hydroureter to the level of the true bony pelvis, and indentation of the bladder by an extrinsic mass. (B) Follow-up intravenous urogram showing resolution of upper tract dilatation after excision of the stricture and the pelvic mass and ureteroneocystostomy.

inflammatory ureteric stricture within the pelvis was present in 2 patients (with pelvic organs that had a relatively normal macroscopic appearance). In the remaining 3 a tubo-ovarian mass with ureteric involvement was found. Resection of the ureteric stricture with primary intubated anastomosis was performed in 3 patients. One had resection of the pelvic mass with ureteroneocystostomy after an unsuccessful trial of danazol, and the last patient had unilateral nephroureterectomy with excision of the pelvic mass. Pathological examination revealed extrinsic endometriosis and dense fibrosis of the ureter in 4 cases and intrinsic ureteric endometriosis with dense ureteric fibrosis in the remaining patient (Fig. 2).

Endometriosis is usually an intraperitoneal disease, but may on occasions be retroperitoneal with extensive fibrosis. Although benign, it may act in a most malignant fashion, involving the bladder or rectum, and this may result in cyclical bleeding at the time of menstruation. Other ectopic sites such as the lungs may be involved, giving rise to cyclical haemoptysis.

The incidence of ureteric involvement by endometriosis is 1.2% (Kerr, 1966). There is usually coexistent involvement of the cardinal and uterosacral ligaments. Only 1 case of ureteric endometriosis above the pelvic brim has been reported (Rosemberg and Jacobs, 1979). Extrinsic ureteric endometriosis is usually secondary to extensive involvement of adjacent pelvic organs, as seen in 3 of our patients. It occurs 4 times as often as the intrinsic form. Both types, however, are found histologically to be present with dense fibrosis. This may be the result of a desmoid type of reaction (Langmade, 1975). Intrinsic endometriosis is characterised by glands and stroma within the lamina propria, tunica muscularis or ureteric lumen.

In many cases it is not possible to identify the cause of ureteric obstruction prior to definitive treatment. The primary aim of surgical treatment is to relieve ureteric obstruction in order to preserve renal function. Because of the dense fibrous tissue reaction that accompanies endometriosis and envelops the ureter, resection of the stricture with primary intubated anastomosis or reimplantation is preferable to ureterolysis. Occasionally, nephroureterectomy is necessary for end-stage disease where no useful renal function remains (as seen in Case 5). The incidence of such silent loss of renal function as a consequence of ureteric endometriosis varies from 25 to 43% (Stillwell *et al.*, 1986).

The secondary aim of treatment is to prevent recurrence of endometriosis; treatment options include short-term measures such as hormonal manipulation using agents such as danazol, though, more recently, LHRH analogues such as buserelin or goserelin have also been tried. This may be continued for up to 6 months but can give rise to menopausal symptoms. Before surgical treatment in the form of hysterectomy with or without bilateral salpingo-oophorectomy is undertaken, an intravenous urogram must be available, especially if there is extensive pelvic fibrotic change or a mass.

This series of patients demonstrates that a diagnosis of ureteric endometriosis must be an early consideration in premenopausal women presenting with loin pain and ureteric obstruction of unknown aetiology within the true pelvis. Early surgical excision of the ureteric stricture allows effective resolution of upper tract obstruction and improved renal salvage.

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Induction of Carcinoma at Ureterosigmoid Anastomosis—with and without Faecal Stream

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Summary—The induction of tumours at the site of uretero-intestinal anastomosis was investigated in Hannover: WISTAR rats. The rats were divided into 3 groups. In one group (n = 70) the ureter of the left kidney was implanted into the colon, using microsurgical techniques developed for humans. In 13% of the rats in this group benign tumours developed; in 16% malignant tumours occurred. In a second group (n = 76) the ureter was implanted into a rectal bladder; the faeces were excluded from the anastomosis by a descending colon anus praeter. In this group benign tumours developed in 17% and malignant tumours in 8%, all of them being situated at the site of the anastomosis. In a control group (n = 80) no colonic tumour could be identified.

To date, 184 tumours after ureterosigmoidostomy have been reported in the literature. To estimate possible tumour induction by urinary diversion only those tumours can be considered as relevant which occur after a benign primary disease. This condition was found in 96 malignant tumours, most of them adenocarcinomas, and 67 benign tumours. The benign tumours were mostly adenomas and, following the adenoma–carcinoma sequence, have to be regarded as pre-cancerous and therefore have to be included (Morson, 1974; Hill, 1978). As was to be expected, the benign tumours developed a decade earlier than the malignant ones. With regard to the benign tumours reported in the literature, the average period of latency was 19 years and 9 months (range 24–588 months); with regard to the malignant tumours it was 27 years and 9 months (range 60–648 months). For 9 malignant and 12 benign tumours ureterosigmoidostomy was performed because of a malignant primary disease. The development of a malignant tumour has also been reported after other forms of urinary diversion: tumours have been found in colocystoplasties, ileocystoplasties as well as in the colon and ileum conduit (Shousha *et al.*, 1978; Chiang *et al.*, 1982; Stöckle *et al.*, 1986). The risk of developing a malignant tumour after ureterosigmoidostomy has to be regarded as approximately 100 to 550 times higher than in the population at large (Urdaneta *et al.*, 1966; Stewart, 1986). Eraklis and Folkman (1978) postulated that the risk was 7000 times higher for patients under 25 years old than for the general population of the same age.

As experimental reports and reviews of the literature still express uncertainty concerning the reason for carcinogenesis after ureterosigmoidostomy, the induction of carcinoma should be tested on animals (Miersch, 1988). In the present study we considered the following.

1. A possible influence on carcinogenesis by altered metabolism should be avoided.
2. By simulating the operation which Hohenfellner (1977) performed on humans, greater validity was assumed than in the simplified models (Crissey *et al.*, 1980; Cohen *et al.*, 1987; Daher *et al.*, 1988).
3. With a larger number of animals the question was whether the induction of carcinomas could only be observed at the site of colonic urinary anastomoses, which are exposed to the faecal stream.
4. The experiment was to include a control group

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of animals that received an exact sham operation. Vasectomy without intestinal irritation—as performed in models so far (Crissey *et al.*, 1980; Aaronson *et al.*, 1987)—does not provide a comparable control group.

Materials and Methods

Male Hannover: WISTAR rates (Han: WIST rats) aged from 6 to 8 weeks were used, each weighing approximately 200 g (Deerberg *et al.*, 1980). To assess the possible effect of altered metabolism, 3 groups of animals underwent surgery and were evaluated.

The first group (I-group, n = 70) underwent ureterosigmoidostomy of the left kidney according to Hohenfellner (1977) (Fig. 1A). Metabolic balance was achieved by the right kidney, which was left *in situ*. By consistent use of microsurgical techniques the operation performed on humans was simulated exactly.

The second group of animals (AP-group, n = 76) received a substitute rectal bladder according to the method of Mauclaire (Fig. 1B). Before urine was introduced into the colon, the faeces were removed completely and the colon was disinfected. The faeces were excluded from the rectal bladder by an anus praeter. Again metabolic balance was achieved by the right kidney remaining *in situ*. Only the ureter of the left kidney was anastomosed to the rectal bladder. The anastomosis was performed as in the I-group. Both groups of animals were controlled by a sham operation group (S-group, n = 80) (Fig. 1C). In this group sigmoidostomy was performed in the same way as in the previous groups. The site of the implantation was altered by forming a submucosal tunnel (Fig. 2). The sigmoidostomy was closed by continuous suture with the same technique used for the other 2 groups.

Six to 8 weeks after the operation an IVU was performed to check the patency of the anastomoses (Fig. 3). Rats with no patent anastomoses were excluded from evaluation. That the metabolism was not disturbed in any of the 3 groups was demonstrated by examining the blood serum (cre-

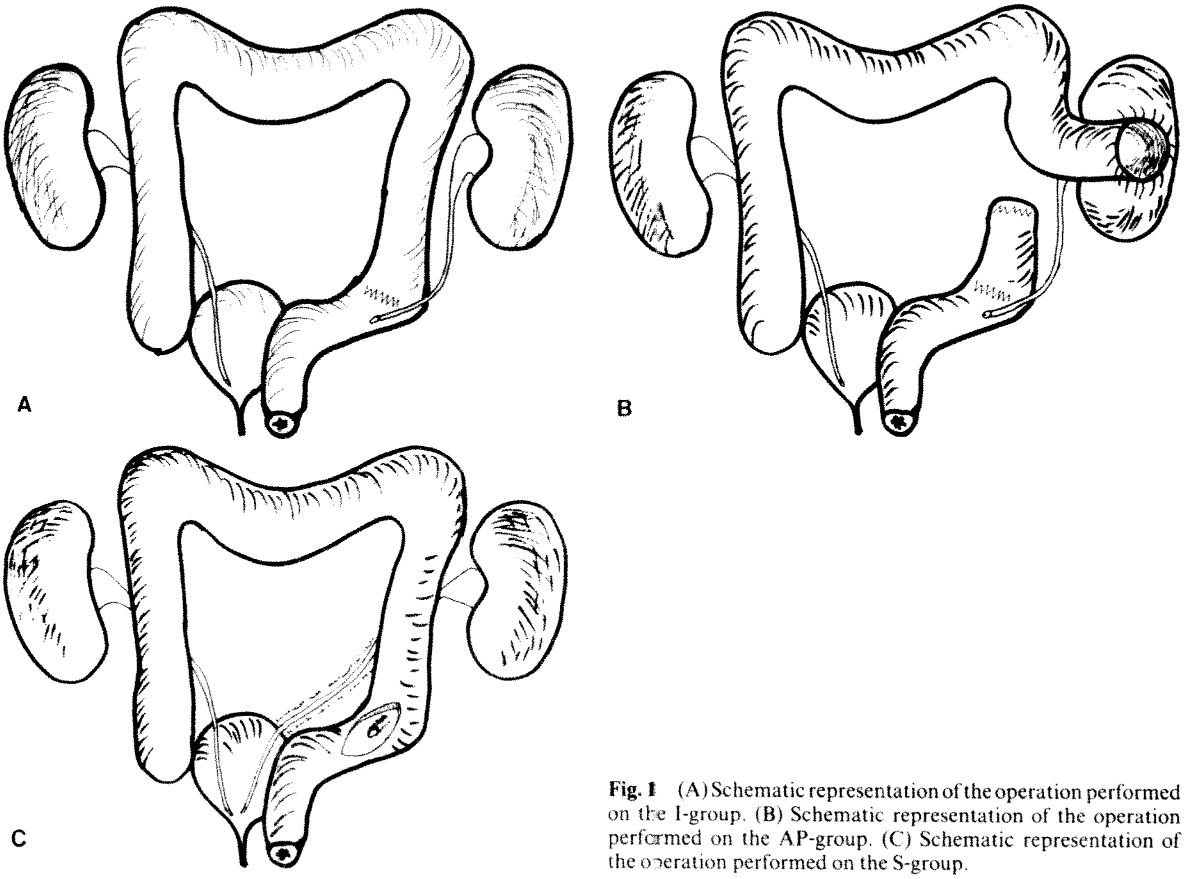

Fig. 1 (A) Schematic representation of the operation performed on the I-group. (B) Schematic representation of the operation performed on the AP-group. (C) Schematic representation of the operation performed on the S-group.

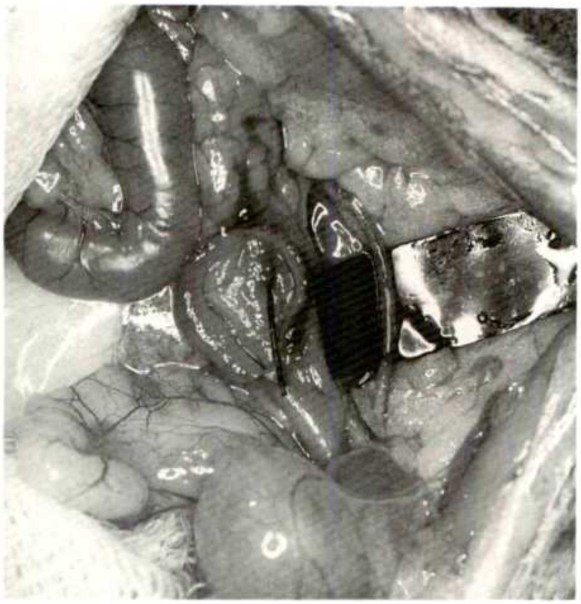

Fig. 2 Site of operation, S-group. Submucosal tunnel marked by thread. Left ureter on plastic sheet.

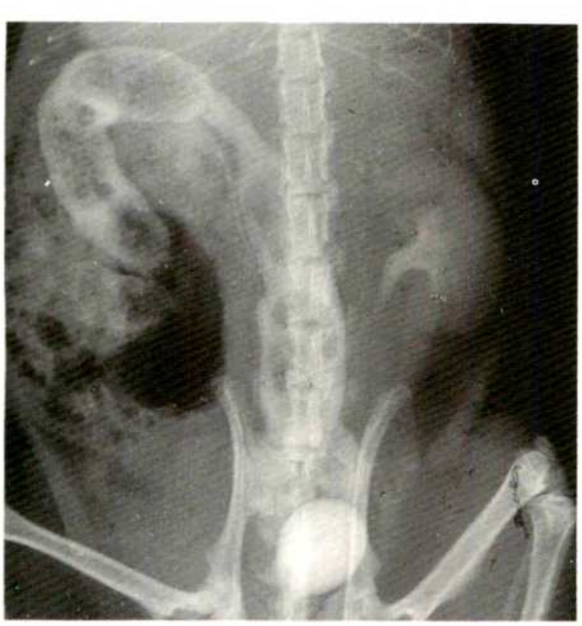

Fig. 3 IVU of an I-group rat. The contrast medium is spread over the surface of the colon.

atinine, electrolytes, blood gas analysis), which were obtained with the puncture for the X-ray examination or partly with the section.

Section was performed when signs of disease were noticed or after a maximal period of 2 years. After the section the animals were examined macroscopically and with the help of magnifying lenses. If tumour formation was seen, a histological examination was performed.

Results

In 35 animals in the I-group (n = 70), tumour formation was found. Histologically in 20 animals neoplasia was seen. This showed a tumour rate of 28.5%. Eleven malignant (16%) and 9 benign (13%) tumours were verified at the site of ureterosigmoidostomy. We found 6 adenocarcinomas (Figs 4A and B) of the intestinal type (9%) and one adenoma (1%). The other tumours were mainly transitional cell carcinomas (7%) and urothelial papillomas (11%) (Figs 5A and B). In almost all of these tumours a distinct admixture of intestinal parts could be found, especially in the base of the tumours. All tumours were directly situated at the site of the anastomosis; no tumour was identified in any other intestinal region. The average post-operative observation period was 19.7 months; for histologically examined rats with malignant tumours the average observation period was 19.4 months.

In the AP-group (n = 76), tumours occurred in 30 animals. Of these, neoplasia was discovered in 19 cases (25%). Malignant tumours at the site of the anastomosis were found in 6 cases (8%). These were polypous transitional cell carcinomas (Figs 6A and B), which developed at the anastomosis and showed a mixture of mucosa and urothelial parts, especially in their base. The benign tumours (17%) comprised 12 urothelial papillomas and 1 adenoma (Fig. 7) of the intestinal type at the site of the anastomosis. Again a mixture containing intestinal mucosa was seen. Here the average post-operative period of observation was 19.9 months. On average, malignant tumours were diagnosed after 22 months, benign tumours after 19.5 months. No tumour was found in the distal region of the rectal bladder.

After an average observation period of 19.1 months, only 1 tumour was found in the S-group (n = 80). It was a malignant germ cell tumour, a kind of teratoma, which was located on the left kidney and had absorbed it almost completely. The tumour developed after approximately 6 months (172 days). No intestinal tumours were identified. Also no change was seen at the site of the previous sigmoidostomy, or mucosal alteration.

All of the other changes which had macroscopically been assessed as tumour could histologically be explained by mucosal hyperplasia, folds of intestinal mucosa or the intestinal wall. In 1 case a small intramural cyst coated with cylindrical epi-

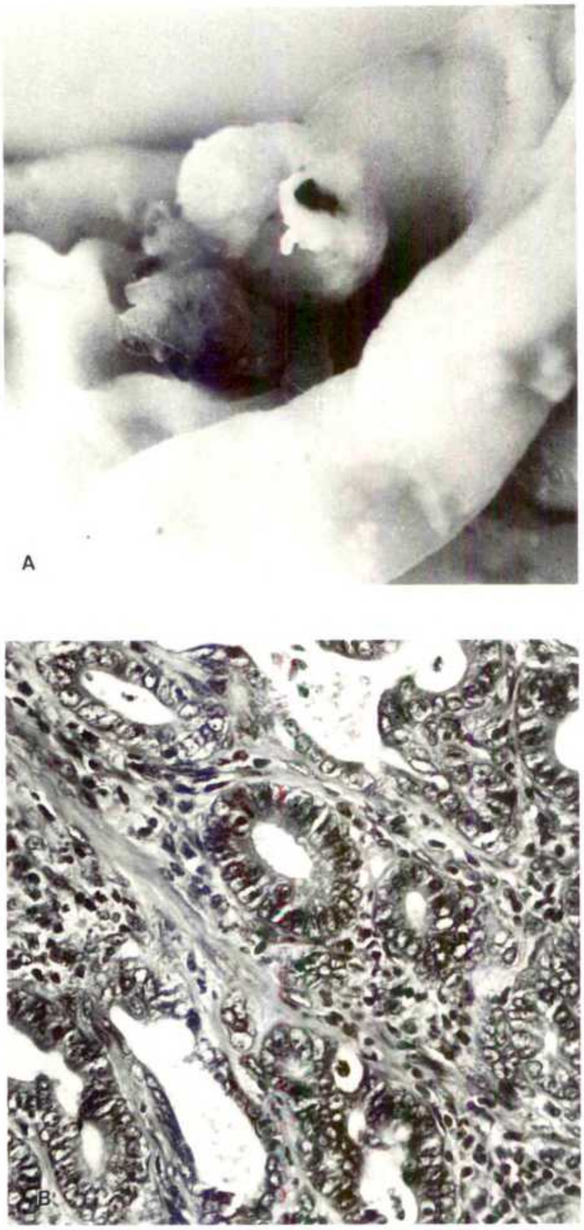

Fig. 4 (A) Macroscopic view of adenocardinoma of intestinal type at the site of ureter implantation. (B) Histological view of adenocarcinoma at the site of ureteric implantation (H and E × 450).

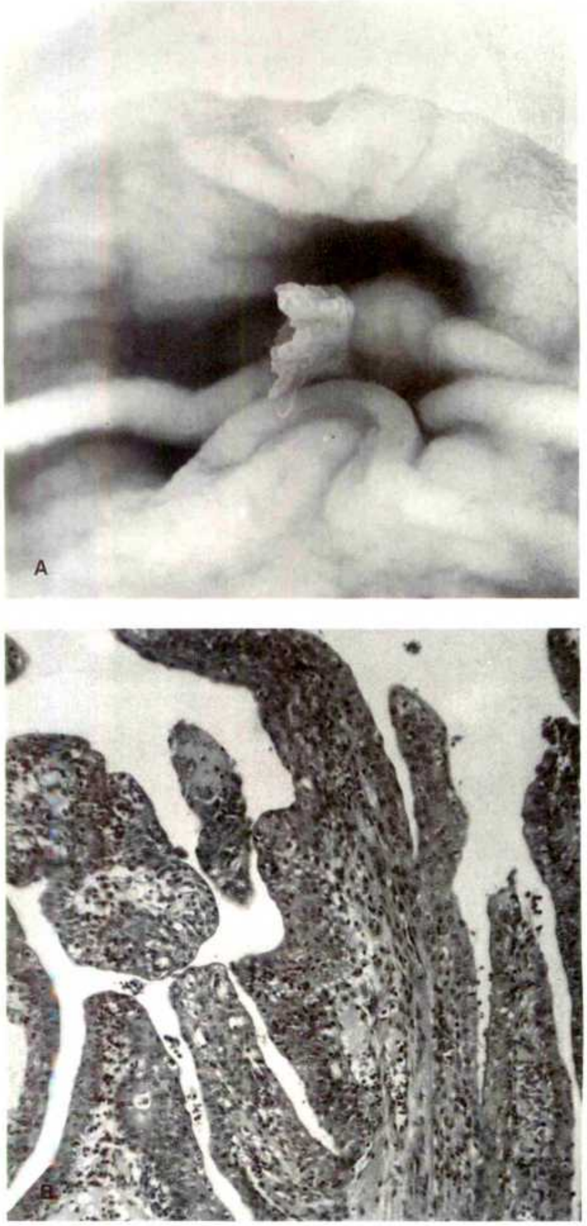

Fig. 5 (A) Macroscopic view of urothelial papilloma at the site of ureteric implantation. (B) Histological view of urothelial papilloma at the site of ureteric implantation. Partially coated with mucosa of colonic type (H and E × 80).

thelium was found. In each case the artificially produced borderline between urothelium and mucosa of the colon turned out to be rather unstable (Fig. 8). Surplus repairs with a mixture of urothelium and mucosa developed at the artificial borderline. The urothelium protruded into the lumen of the bowel as far as possible and the mucosa of the colon seemed to coat the lumen of the ureter.

Discussion

These results reveal induction of carcinoma at the site of the implantation with or without faecal stream. With a combined diversion of both urine and faeces transitional cell carcinoma occurred in 7% and adenocarcinoma of the intestinal type in 9%. When only urine entered the colon, transitional

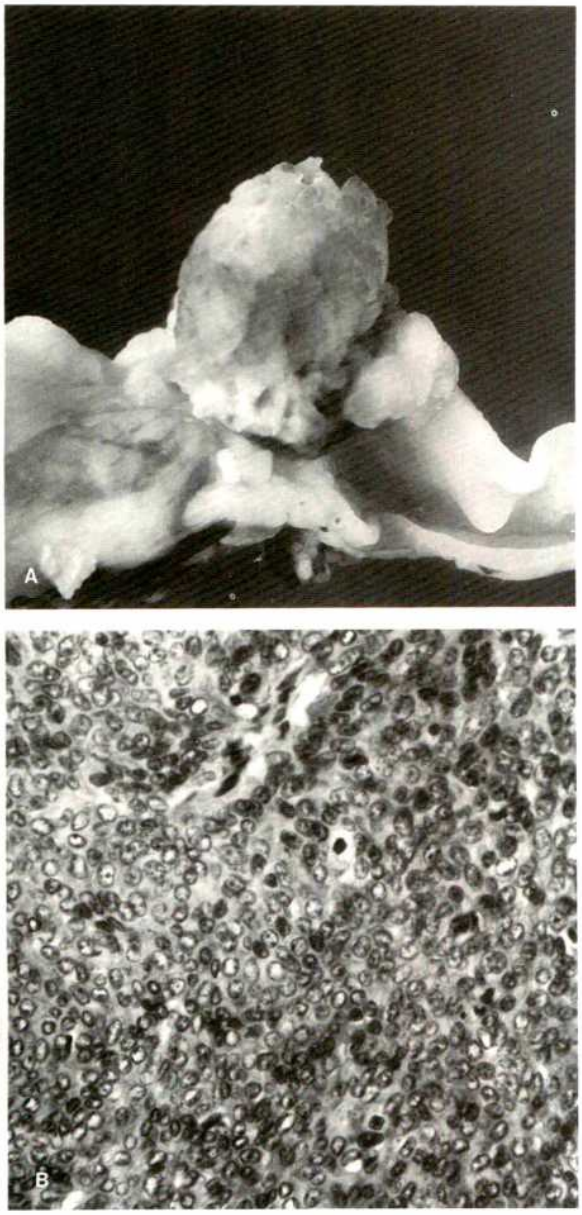

Fig. 6 (A) Macroscopic view of transitional cell carcinoma at the site of ureter implantation. (B) Histological view of transitional cell carcinoma at the site of ureter implantation. (× 450; HE stain.)

cell carcinomas occurred in 8%. One adenoma of intestinal type was seen. Deerberg *et al.* (1980) reported no spontaneous incidence of these tumours when examining their Han: WIST rats of a similar age.

Aaronson *et al.* (1984, 1987) postulated that the origin of the adenocarcinomas in ureterosigmoidostomies may be the dysplastic urothelium.

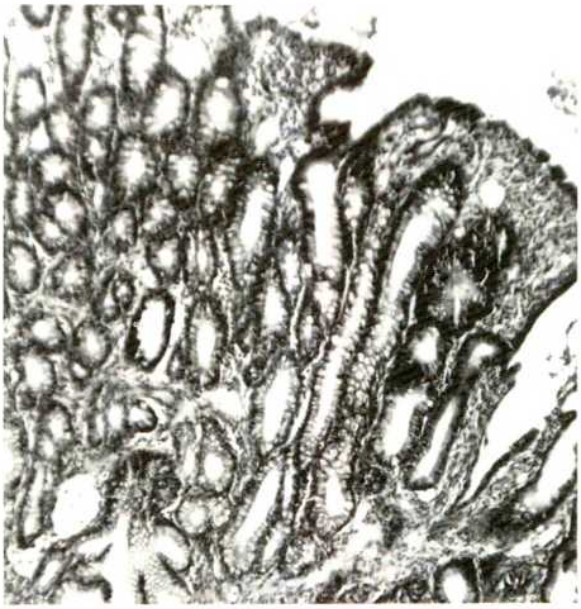

Fig. 7 AP-group. Histological view of adenoma at the site of ureter implantation. (× 250; HE stain.)

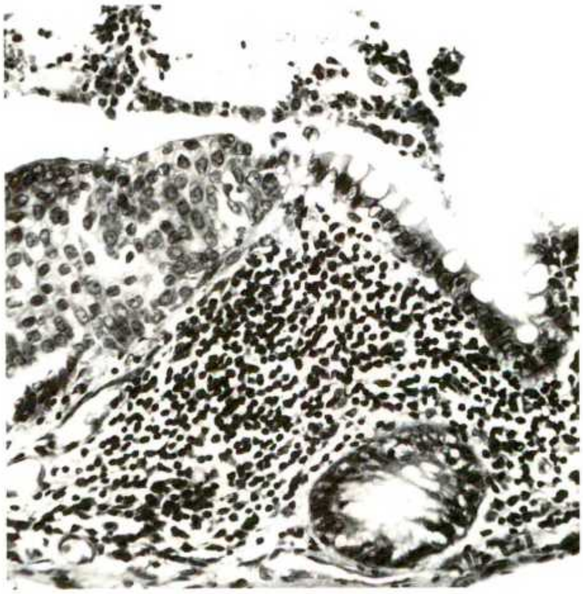

Fig. 8 Artificially produced, unstable borderline between urothelium and mucosa. Lymphocyte infiltration in subepithelial stroma. Rests of colonic crypts. (× 250; HE stain.)

Other experimental reports confirm the induction of transitional cell carcinoma by chronic irritation of the transitional cell epithelium (Chapman *et al.*, 1973; Harzmann *et al.*, 1983).

Attempts have been made to explain the induction of carcinoma after ureterosigmoidostomy.

Aldis (1961) regarded the mechanical trauma produced by projecting ureteric nipples in the colon as a responsible factor. Bristol and Williamson (1981) found the trauma resulting from the surgical suture to be the reason. According to Mostofi *et al.* (1955) the reason for carcinogenesis was chronic irritation leading to metaplasia and finally to carcinoma. Aaronson *et al.* (1987) supported this theory. Crissey *et al.* (1980), however, regarded faecal carcinogens as the cause and implicated N-nitrosamines. In their simplified rat model 4 of 6 rats developed an adenocarcinoma. Vasectomised rats served as a control group. Other authors continued with this model and reported up to 80% of tumours (Gittes, 1986; Daher *et al.*, 1988).

Harguindey *et al.* (1976) suggested that irritation produced by the excessive concentration of electrolytes was responsible for carcinogenesis. Culp (1964) assumed that the change in the histology of the dysplastic transitional epithelium in patients with exstrophy of the bladder relevant to the induction of carcinoma.

Stewart (1986) postulated the development of carcinogenous N-nitrosamines, which originate from the nitrate of the urine and are reduced to nitrite by bacterial mixed flora and contact with faeces. Stewart assumed that these N-nitrosamines may be the reason for carcinoma after ureterosigmoidostomy.

Using a more precise method, Kälble *et al.* (1990), in contrast to Cohen *et al.* (1987), did not find a significant difference in the formation of N-nitrosamines with and without urinary diversion. With regard to our own results—8% of malignant tumours at the site of the anastomosis without faecal contact—it is interesting that according to Stewart (1986) N-nitrosamines may also develop in conduits. The local effect of the junction of colonic mucosa and transitional cell epithelium is underestimated. As the IVUs taken from our surgically treated rats proved, a prompt intermixture of both urine and faeces is achieved throughout the whole colon within a few minutes (Fig. 3). Therefore it is not to be expected that N-nitrosamines will develop only at the site of the anastomosis or that the concentration of N-nitrosamines will vary substantially within the whole colon. It is more likely to find a more even distribution of carcinomas throughout the whole colonic surface, perhaps with an increasing amount towards the anastomosis. Yet all carcinomas described in the literature occurred adjacent to the site of the implantation of the ureter and seemed to result from the artificial borderline. In other regions of the sigmoid which were also irritated surgically not a single carcinoma could be found. We therefore conclude that neither the carcinogenous N-nitrosamines nor the surgical irritation alone explain carcinogenesis.

We found an extremely unstable borderline of transitional cell epithelium and intestinal mucosa with regenerating activity raised to a maximum (Fig. 8). The mucosa of the colon often coated the ureter, while the transitional cell epithelium often extended beyond the implantation site and protruded into the colon. In the course of time this instability led to hyperplasia, adenomatous changes with atypia and finally to carcinoma. Other factors such as metabolism, possible carcinogens, and mechanical irritation may contribute to the development of carcinoma. The importance of the metabolism was also shown by our model. Here a tumour rate of 16%, which still shows a clear increase, compares with an incidence of 60–80% with metabolism left unbalanced (Crissey *et al.*, 1980; Gittes, 1986).

It should also be considered whether, compared with the high level of nitrite in our food, the amount of the absorbable nitrate which is discharged with the urine may be small, so that finally even without ureterosigmoidostomy the development of N-nitrosamines should be possible with the existence of faeces, nitrate and a bacterial mixed flora. Relevant data, especially those taking diet and nitrate level into account, have not been published so far and are to be the matter of further research.

Some case reports dealing with the induction of tumours after ureterosigmoidostomy pointed out that ureterosigmoidostomy had been converted into another urinary diversion after some time (Eraklis and Folkman, 1978; Schipper and Decter, 1981; Uehling *et al.*, 1982; Starling *et al.*, 1984; Schwab *et al.*, 1986; Miersch *et al.*, 1989). If—as mentioned in these cases—ureteric stumps were left in the sigmoid, the missing urine would not influence and prevent the development of neoplasia. Carcinomas (n = 13) occurred after an average period of 23 years and 10 months, ranging between 177 and 360 months. So in this small number of patients the period of latency was reduced by 4 years compared with the general course of induction of tumour.

It is striking that metabolic alterations in the form of hyperchloraemic acidosis and recurrent pyelonephritis or congestion of the upper urinary passages always led to a conversion of ureterosigmoidostomy into another form of urinary diversion. The reciprocal influence of these complications, especially the increased alteration of the metabolism with urinary obstruction after urinary diversions into the bowel segments, is well known (Zacher *et al.*, 1983). The examples show the necessity of removing the colon segment with the ureteric implantation when conversion into another diversion is performed, even though urologists avoid this step to prevent a more extensive operation. It is also important to keep these patients under regular follow-up. It is indisputable that early and lifelong endoscopic follow-up of patients with ureterosigmoidostomy is necessary (Jones *et al.*, 1980; Uehling *et al.*, 1982; Starling *et al.*, 1984; Martinez *et al.*, 1986). Tests should also be carried out to discover occult blood in the faeces (Hardcastle *et al.*, 1980). Radiological controls alone do not seem to be sufficient (Amis *et al.*, 1981). Furthermore, these patients need regular control of their metabolic process and optimal regulation.

As the tumours in the rectal bladder show in our rat model, the requirements mentioned above must also be applied to all patients having any urinary diversion incorporating the bowel—especially the colon.

The following conclusions have been made.

1. All urinary diversions incorporating the bowel, at least all colonic urinary diversions, must be kept under regular endoscopic control. This is also required for those urinary diversions that exclude the faecal stream.
2. The colon should only be used for urinary diversion with stringent safeguards.
3. If possible, all polyps should be removed endoscopically. An exact histological diagnosis is necessary.
4. With recurring adenomas, ureterosigmoidostomy must be converted and the affected colon, including the site of the ureteric implantation, resected. Whenever ureterosigmoidostomy is converted into another urinary diversion, the colon segment with the site of the ureteric implantation must be resected, too.
5. Patients with ureterosigmoidostomy need regular follow-up examinations; their metabolism must be balanced precisely.
6. The unstable, artificially produced borderline between transitional cell epithelium and mucosa of the colon which is exposed to additional irritation (mechanical irritation, carcinogens, concentration of electrolytes, altered metabolism), seems to be an important local factor for the induction of carcinoma.

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Anti-reflux Surgery by Injection of Teflon Paste

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Summary—Over a 3-year period, 55 refluxing ureters in 36 patients were treated by the endoscopic injection of Teflon paste. Although reflux was corrected immediately in 54 ureters (98%), reflux recurred 3 to 4 months later in 18 ureters. Reinjection was carried out once in 5 ureters and twice in 1. The success rate was 71% in primary reflux and 53% in secondary reflux.

Significant side effects were encountered post-operatively in 3 patients: vesicoureteric junction obstruction in 2 and urethral stricture in 1. We recommend that the results of surgery should not be evaluated until at least 3 to 4 months after operation. A review of the literature shows that the overall success rate was 92% in 367 ureters with primary reflux and 70% in 181 ureters with secondary reflux. Because of the uncertain outcome of surgery and the possibility of adverse side effects, one should be cautious when considering this form of treatment in young children.

Correction of vesicoureteric reflux (VUR) by the endoscopic injection of polytetrafluoroethylene (Teflon) paste was first described by Matouschek (1981) and its effectiveness was confirmed by Puri and O'Donnell (1984) in 8 piglets and subsequently in 13 girls (O'Donnell and Puri, 1984). Since then, more than 10 reports have described similarly satisfactory results with few complications. We record our experience with this form of treatment and collate all reported results to date.

Patients and Methods

We reviewed all patients with primary or secondary VUR treated in this unit by the endoscopic injection of Teflon paste from August 1987 to July 1990. Pre-operative VUR was graded as recommended by the International Reflux Study Committee (1981).

In children and adult females the procedure was conducted using 5 F tubing with a 10 mm long, 22 gauge needle passed via a 14 F cystoscope; with adult males, 9 F tubing with a 20 mm long, 18 gauge needle was used and passed via a 21 F cystoscope. The injection technique was as described by O'Donnell and Puri (1984, 1988); the needle, penetrating the bladder mucosa 5 mm below the ureteric orifice, was advanced 10 mm obliquely and then gradually withdrawn as the Teflon paste was injected, so that the initially gaping ureteric orifice assumed a flattened, crescentic configuration. The amount of Teflon injected varied from 0.5 to 2.0 ml (mean 1.0). Expression cystography was performed upon completion of the procedure. Micturating cystourethrography (plus ultrasonography of the renal tracts) was undertaken 3 to 4 months post-operatively. The procedure was rated successful if the latter cystogram showed resolution of VUR or persisting VUR no greater than Grade I.

Results

During the study period we treated 37 patients by endoscopic injection of Teflon paste and follow-up was available in 36 instances (22 females, 14 males). Their ages, at the time of the procedure, ranged from 2 to 59 years (mean 16); 19 were children under 10 years of age; 24 patients (38 ureters) had primary VUR and 12 (17 ureters) secondary VUR due to neuropathic bladder (8 congenital cord lesions, 4 traumatic cord lesions).

The pre-operative grades of VUR, together with success rates on cystography 3 to 4 months post-

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operatively, are shown in Table 1. Although expression cystography immediately after operation showed resolution of VUR in 54/55 instances (98%), recurrence of VUR was evident in 18 instances 3 to 4 months post-operatively. In 3 patients with neuropathic bladder there was fresh, contralateral VUR. In 4 patients with a satisfactory result at 3 to 4 months, further cystography at 12 to 25 months showed no example of recurrent VUR.

In 6 failed cases, reinjection was carried out, once in 5 and twice in 1; in 4 cases VUR has since resolved. In 5 other patients (2 primary VUR, 3 secondary VUR), successful open surgical correction of VUR was achieved following failure of Teflon paste injection.

Post-operative complications occurred in 3 cases: 2 patients (2 ureters) developed secondary vesicoureteric junction obstruction, requiring percutaneous nephrostomy drainage for 25 and 26 days, and one 5-year-old boy developed a bulbar urethral stricture that required urethrotomy.

The results of other reported series of Teflon paste injections are summarised in Table 2.

Discussion

The rationale of Teflon paste injection is to buttress the ureter in the intramural space and/or to compress its most distal portion. In this series, as in others, the procedure seems more suited to primary VUR; in all reported series the success with primary VUR (92%) significantly exceeded that with secondary VUR (70%) ($P < 0.01$). Nonetheless our results with both forms of VUR have been appreciably inferior to those reported by other workers. One reason might be that in some series cystography was performed a very short time after operation. In our experience this is unsatisfac-

Table 1 Results in 55 Ureters 3 to 4 Months after Surgery

		Primary reflux		*Secondary reflux*	
Grade	*No. of ureters*	*Success*	*Failure*	*Success*	*Failure*
1	6	3	2		1
2	16	7	2	6	1
3	10	5		2	3
4	15	8	4	1	2
5	8	4	3		1
	55	27 (71%)	11	9 (53%)	8

Table 2 Review of the Literature

	Success rate (no. of success/total no.)	
Author(s)	*Primary reflux*	*Secondary reflux*
Matouschek (1981)	1/1	
O'Donnell and Puri (1984)	17/18	
Puri and Guiney (1986)		13/15
O'Donnell and Puri (1986)	116/130	11/20
Schulman *et al.* (1987)	35/36	
Kaplan *et al.* (1987)	19/20	15/20
Diamond and Boston (1987)		1/1
Quinn *et al.* (1988)		37/41
King and Gollow (1988)	35/36	
Yachia (1989)	4/4	4/7
Farkas *et al.* (1990)	83/84	21/31
Dewan and Guiney (1990)		16/29
Present series	27/38	9/17
Total	337/367 (92%)	127/181 (70%)

Secondary reflux includes duplex systems, megaureters, ureteroceles, failed operations and neurogenic bladders.

tory and cystographic reassessment should be delayed for 3 to 4 months post-operatively. Limited experience indicates that VUR is unlikely to recur after this interval. On the other hand, we found that the results of reinjection appreciably exceeded the 10 to 20% success rate described in other series.

Previous reports of complications have been few, comprising 2 cases of secondary vesicoureteric junction obstruction (Puri and Guiney, 1986; Kaplan *et al.*, 1987) and 1 of septicaemia (Quinn *et al.*, 1988). The present series doubles that number. Secondary vesicoureteric obstruction is theoretically avoidable by not advancing the needle too far and not injecting too much Teflon paste; once established, this complication seems transient and manageable by a period of percutaneous nephrostomy drainage or insertion of a ureteric splint. Urethral stricture is potentially a complication of any transurethral procedure in a male subject.

Since 1987 our enthusiasm for this form of treatment has waned. Our success rate is less than that reported by others and is inferior to the results of open surgical correction. The advantages (no invasive surgery, minimal pain, shorter hospital stay) must be weighed against the relatively uncertain outcome, risk of complications and necessity for secondary procedures, and we feel it important that patients (or parents) should be made aware of these factors before deciding upon treatment.

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Abscess of Urachal Remnant Mimicking Urinary Bladder Neoplasm

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Summary—Three cases of urachal abscess with extensive interstitial inflammation and fibrosis are reported. Clinically, all patients had a lower abdominal mass and CT scan and ultrasonic examination revealed a large tumour located anterior or superior to the bladder. They all underwent laparotomy and had either a partial cystectomy or an *en bloc* resection of the bladder and adjacent organs due to severe adhesions. Microscopic examination of the specimens revealed no evidence of carcinoma and only abscess formation with extensive chronic interstitial inflammation and fibrosis were seen. In one case, residual columnar epithelium suggestive of urachal origin was identified in the abscess cavity. Urachal abscess should be considered when dealing with lower abdominal masses.

Although infection of a urachal cyst or diverticulum is known to occur, there have been no reports of abscesses of the urachal remnant mimicking bladder tumours. Even sophisticated diagnostic procedures, such as CT scans, cannot always distinguish between urachal abscess and carcinoma. Multiple biopsies should be performed to exclude carcinoma. In the last 2 years we have encountered 3 patients suspected of having carcinoma of urachal origin, but all proved to have an abscess of the urachal remnant with extensive interstitial inflammation and fibrosis.

Case Reports

Case 1. A 48-year-old woman was referred with a lower abdominal mass. One year earlier she had been diagnosed as having uterine fibroids and a laparotomy had been performed. No radical operation was carried out because she was found to have a "bladder tumour". Cystoscopic examination showed a bulging mass 3 cm in diameter at the dome of the bladder. Computed tomography revealed an irregular 3-cm mass on the anterior aspect of the bladder with a markedly thickened wall (Fig. 1). An irregular 2.5-cm mass was also noted anterior to the bladder at the level of the femoral head suggesting extravesical extension of a urachal carcinoma. Bladder biopsy was not diagnostic as only oedematous thickened mucosal wall was seen. Owing to severe adhesions in the pelvis, only a partial cystectomy was performed. A mass about 6 cm in diameter was located at the dome of the

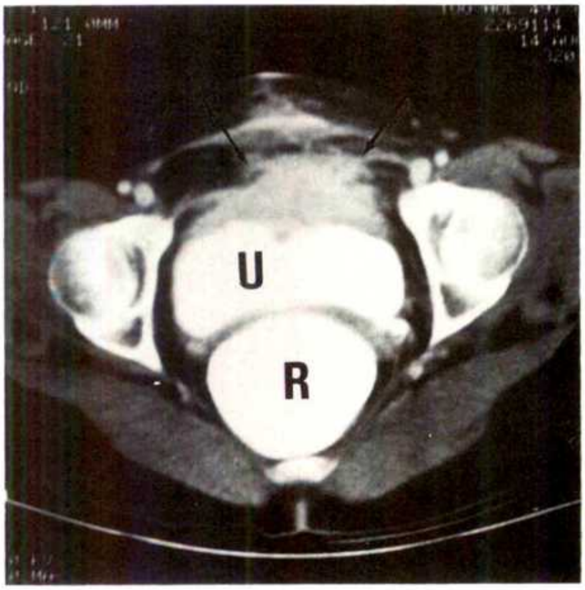

Fig. 1 Ct scan shows an irregular mass contiguous with the urinary bladder (arrows). R: rectum. U: urnary bladder.

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bladder, markedly adherent to the pelvic bone, perivesical tissue and muscles. Microscopic examination of the partially resected bladder revealed marked thickening of the bladder wall with severe interstitial inflammation; adjacent to the external surface of the bladder was a necrotic ulcer with abscess formation but no tumour was identified. The patient's post-operative course was uneventful and subsequent IVU, bone scan, chest X-ray and blood tests were all normal. The patient was well 2 years after surgery.

Case 2. A 39-year-old woman was well until 4 months prior to admission, when she began to experience dysuria. Ultrasonography and IVU disclosed a bladder tumour. She was then referred to this hospital. Cystoscopy revealed a large mass at the dome of the bladder and believing it to be a bladder tumour, a radical cystectomy was performed; a large mass occupying the anterior aspect of the bladder extending along the urachus was found. The entire specimen, including the bladder, posterior urethra, uterus, tubes, ovaries, anterior rectus muscle and urachus with umbilicus were removed *en bloc*. Multiple sections of the specimen revealed an abscess cavity located at the dome, within a thickened bladder wall. A focus of residual columnar epithelium was seen on the cavity wall, suggestive of a urachal origin (Fig. 2). No evidence of carcinoma was seen. The patient's post-operative course was uneventful and she was well 2 years after surgery.

Case 3. This 74-year-old man was well until 20 days prior to admission, when he began to suffer from constipation and difficult urination. At another hospital a large pelvic mass measuring 20 × 20 cm was found and he was referred to this centre. Abdominal sonograhy revealed a heterogeneous mass with mixed echogenicity, located posterior and superior to the urinary bladder (Fig. 3). Abdominal CT scan also showed a large tumour 15 × 14 × 9 cm adherent to the bladder wall, which was markedly thickened. This mass also appeared to invade the transverse colon, part of the mesentery and the small bowel wall. Prostatic hypertrophy and bilateral hydronephrosis were also noted. Because of severe adhesions to the pelvic wall, small bowel and transverse colon, only a partial cystectomy was done. Microscopically, the cyst wall showed fibrosis with marked chronic inflammatory cell infiltrate, capillary proliferation, haemorrhage and sheets of foamy histiocytes (Fig. 4). The post-operative course was uneventful. Follow-up sonography showed marked irregular thickening of the bladder wall. The patient was well 1 year after surgery.

Discussion

The urachus is found at the apical portion of the bladder and forms a fibromuscular strand between the apex of the bladder and the umbilicus. Failure to obliterate the lumen of the allantois may result in one of the following abnormalities (Agatstein and Stabile, 1984): patent urachus or vesicocutaneous fistula; urachal sinus at the umbilicus; vesicourachal diverticulum; urachal cyst; alternating sinus.

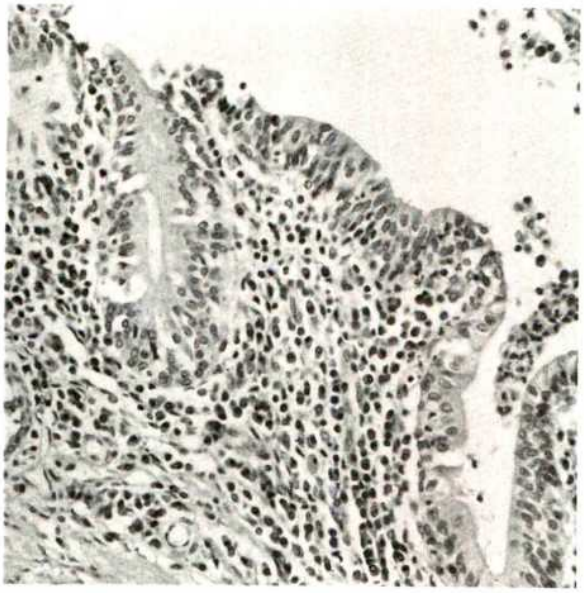

Fig. 2 Within the abscess in the thickened bladder wall there is a focus of columnar epithelium lining the cavity. (H and E × 250).

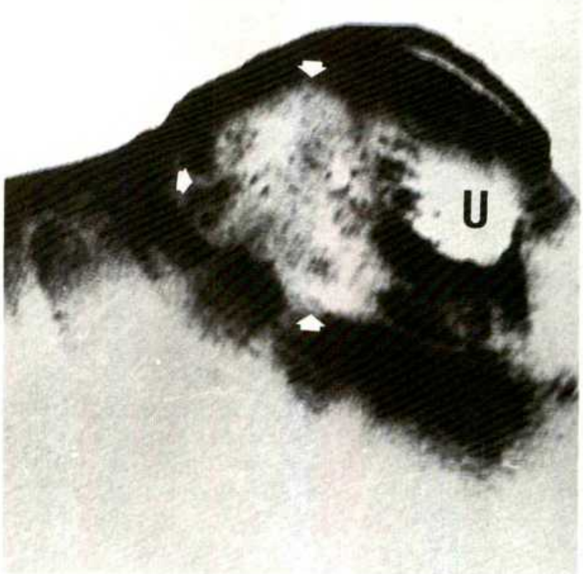

Fig. 3 Sonography with sagittal scan at the middle of the lower abdomen shows a heterogeneous mass (white arrows) with mixed echogenicity located posterior and superior to the urinary bladder (U).

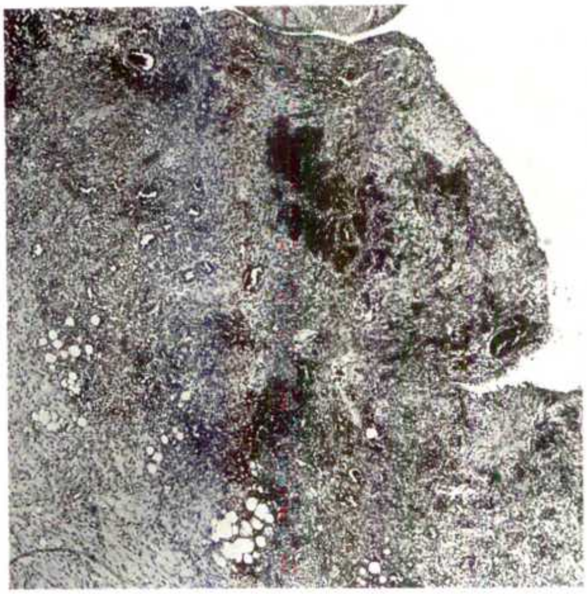

Fig. 4 The cyst wall shows fibrosis with marked chronic inflammatory cell infiltrate, capillary proliferation and haemorrhage (H and E × 125).

In addition to infection, primary carcinoma may arise from this remnant, although this is relatively rare. If a tumour arises from the dome or anterior wall of the bladder, it is often regarded as a carcinoma of urachal origin. In this situation, cystoscopic examination and mucosal biopsy may not be helpful in making the diagnosis. Inflammation of this urachal remnant demands attention because of its clinical resemblance to carcinoma of the urachal remnant. Because the mass usually extends into the bladder wall, it may present as a bulging mass within the bladder and covered by oedematous mucosa.

Urachal cysts (Agatstein and Stabile, 1984; Jordan *et al.*, 1961; Schubert *et al.*, 1982) and carcinoma (Ghazizadeh *et al.*, 1983; Kakizoe *et al.*, 1983; Sheldon *et al.*, 1984) can usually be differentiated by careful physical examination. Agatstein and Stabile (1984) reported 4 cases of peritonitis due to intraperitoneal perforation of infected urachal cysts. In the setting of acute lower abdominal peritonitis, the presence of a lower midline mass, an umbilical discharge or a concomitant urinary tract infection should suggest the possibility of a urachal lesion.

An infected urachal cyst with a prevesical abscess has been reported by Borten and Friedman (1984). Recent reports indicate that with the wider usage of CT scans, some silent urachal abnormalities can be identified (Jordan *et al.*, 1961).

Apart from urachal cysts or diverticula, the major problem arising from the urachus is a neoplasm, usually adenocarcinoma. Ghazizadeh *et al.* (1983) reported that there were 154 cases of urachal carcinoma in the English literature and 157 in the Japanese literature up to 1983. Urachal carcinoma accounts for 0.07 to 0.70% of bladder tumours in western countries, and 0.55 to 1.2% in Japan.

The 3 patients reported here demonstrate that a urachal abscess which extends into the bladder wall may resemble a urachal carcinoma. The surgeon and pathologist should try to identify the inflammatory nature of the lesion. Multiple frozen section examinations during the operation may help to exclude urachal carcinoma and avoid an unnecessary *en bloc* resection.

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Continent Urinary Reservoirs

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Summary—We report our experience of 30 continent urinary reservoirs (CURs) after radical cystectomy. The patients ranged in age from 35 to 70 years. There were 22 males and 8 females. Pre-operative urograms showed normal upper tracts in 22 patients, unilateral hydronephrosis in 4 and bilateral hydronephrosis in 4. The first 20 patients had a standard CUR procedure and the last 10 had a modified CUR. The mean operative time, blood loss and post-operative stay were 6.6 h, 900 ml and 25 days respectively for standard CURs and 5.7 h, 825 ml and 21 days respectively for the modified CURs. Post-operatively, urinary leaks from the caecostomy site occurred in 2 patients (1 of which was fatal) while 3 other patients had prolonged ileus, burst abdomen and intestinal obstruction probably due to non-demonstrable urinary leaks. All 5 complications occurred in the first 20 patients. Upper tract status was evaluated in 28 patients 3 months after surgery and showed normal upper tracts in 19 patients, improvement in 6 (35%) and worsening in 3 (12.5%). Pouchograms showed no reflux in 25 patients, unilateral reflux in 2 and bilateral reflux in 1. Complete continence was achieved in 25 patients—2 of them had revision surgery, giving a success rate of 89% with a follow-up of 6 to 48 months (median 24). The remaining 3 patients were incontinent.

Radical cystectomy has been the treatment of choice for muscle-invasive tumours of the bladder (Whitmore, 1978), with or without prior radiation therapy (Montie *et al.*, 1980), at the majority of centres in the world. This operation is necessarily followed by a urinary diversion. Bricker's (1950) ileal conduit has been the most popular diversion but it involves management of the stoma and an external appliance and is not without long-term complications (Pitts and Muecke, 1979). During the past decade a changed approach towards continent urinary reservoirs has emerged which is undoubtedly better accepted by patients (Kock *et al.*, 1982; Skinner *et al.*, 1984; Rowland *et al.*, 1985).

For over 10 years we have perfected our technique of ileal conduit, leading to excellent patient compliance and improved survival rates. A recent report on continent urinary reservoirs (Rowland *et al.*, 1987) led us to undertake the operations reported here.

Patients and Methods

A total of 108 patients underwent radical cystectomy for infiltrating bladder cancer during a 4-year period between January 1987 and December 1990, of whom 30 had continent urinary reservoirs. The indications for cystectomy were standard but these patients had to satisfy the following criteria before being offered a continent urinary diversion: (1) high motivation, (2) age less than 70 years, (3) absence of severe systemic medical problems. All patients were informed about the surgery and the various alternatives available by the staff urologist and the enterostomal therapist.

The pre-operative investigation of these patients included a detailed history and physical examination, haematocrit, renal biochemistry and liver profile. The status of the upper tracts was established by intravenous urography and isotope renography. The local extent of the disease was delineated using computed tomography or ultrasonography. Distant spread of the disease was excluded by chest X-ray and isotope bone scan. All patients were subjected to cystoscopy and biopsy of the

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tumour and bimanual examination under anaesthesia by a staff urologist. A 1-stage standard radical cystectomy with continent urinary reservoir was done in all 30 patients. The first 20 patients had the standard procedure of caecoileal urinary reservoir (Indiana pouch) as described by Rowland *et al.* (1985). Subsequently, we modified the procedure in the last 10 patients. The modifications were: (1) opening the colon along the anterior taenia as far as the level of the caecum (Fig. 1A, B); (2) excising a 0.5 cm disc of mucosa on the posterior wall of the isolated colon and developing a submucosal tunnel, through which the ureters were delivered in the colonic cavity by a "pull-through" method (Fig. 1C); (3) ureterocolonic anastomosis was done with interrupted 4/0 vicryl sutures, and Wygon catheters Nos 6–8 were used as stents (Fig. 1C); (4) appendicectomy was done leaving a 0.5 cm stump which was used to put the caecostomy catheter (22 F Malecot) from inside out, and a purse string suture was used to fix the catheter; (5) the pouch was closed by suturing the posterior and anterior wall horizontally in 1 layer with vicryl continuous sutures (Fig. 1D); (6) the ileum was plicated over a 12 F Foley catheter and was brought out as a cutaneous stoma.

All patients received a combination of cephalosporins and aminoglycosides in the post-operative period for 7 to 10 days. The caecostomy and the ureteric stents were removed after a caecogram 3 weeks later. The patients were taught self-catheterisation every 2 to 4 h after the caecostomy tube was removed. The results of the urinary diversion were assessed 3 months after surgery. All patients were followed up at 3-monthly intervals for the first 2 years and every 6 months thereafter. Follow-up ranged from 6 to 48 months (median 24).

Results

A total of 108 cystectomies were performed for infiltrating bladder cancer. Post-cystectomy urinary diversions were continent urinary reservoirs in 30 patients, neobladders in 28 and ileal conduits in 50 patients. Further analysis is limited to the 30 patients with CURs. The youngest and the oldest patients were 35 and 70 years respectively. There were 22 males and 8 females. Pre-operative urograms showed normal upper tracts in 22 patients (44 units), unilateral hydronephrosis in 4 patients (4 units) and bilateral hydronephrosis in 4 patients (8 units), 2 of whom required percutaneous nephrostomies prior to cystectomy. Staging in these patients was B1 in 2, B2 in 21, C in 6 and D1 in 1 patient. Pre-operatively, 7 had received radiation therapy (20–50 Gy) and 3 received M-VAC chemotherapy. Of the remaining 20 patients, 17 had no prior treatment and the remaining 3 had salvage cystectomies for residual disease after radical radiation therapy. Histologically, the tumours were transitional cell carcinoma in 25 patients, transitional with squamous carcinoma in 2, adenocarcinoma in 2 and anaplastic carcinoma in the remaining patient. Eleven patients had Grade II and 19 had Grade III lesions. Table 1 summarises the CUR data and complications. A standard CUR operation

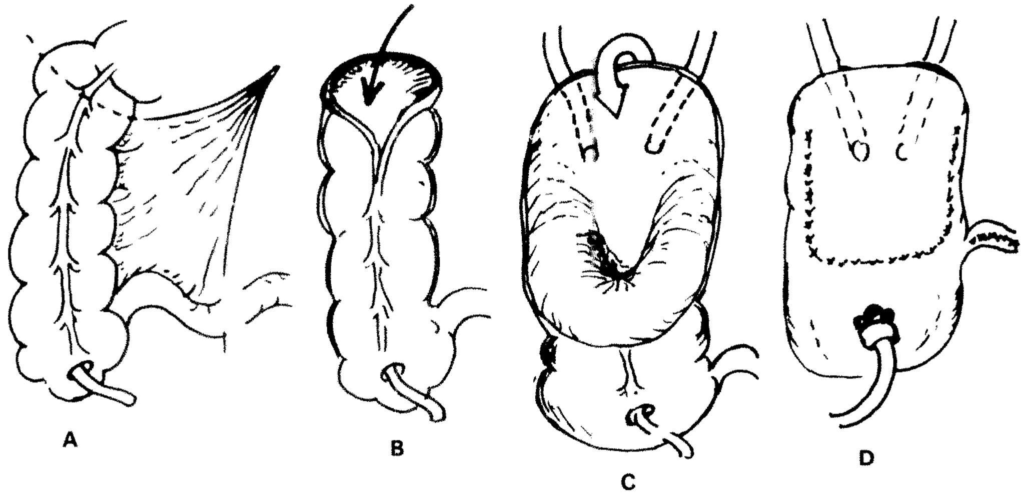

Fig. 1 Technical details of modified CUR: (A) isolation of the ileocolonic segment; (B) opening the colon along the anterior taenia; (C) open uretero-colonic anastomosis and appendicectomy leaving the stump behind; (D) the completed pouch with indwelling caecostomy.

Table 1 Operative Data and Complications of CUR

Continent urinary reservoirs (n = 30)
Standard (n = 20)
Modified (n = 10)

	Standard	*Modified*
Mean operative time (h)	6.6	5.7
Mean blood loss (ml)	900	825
Median post-operative stay (days)	25	21
Complications:		
Suspected urinary leaks	5	0
(a) Caecostomy site*	2	0
(b) Non-demonstrable	3	0
ileus	1	—
wound dehiscence	1	—
intestinal obstruction	1	—
Fever and urinary tract infection	2	0
Minor wound infection	1	1
Hyperchloraemic acidosis	1	0

* One patient died from septicaemia, the other was salvaged.

was performed in the first 20 patients and the last 10 had our modified CUR operation. The mean operative time was 6.6 h for the standard CUR operation (inclusive of cystectomy) and this was reduced by about 1 h in the case of modified CUR operations. The mean operative blood loss was about 900 ml for the standard CURs and 825 ml for the modified ones.

Amongst the early complications urinary leak was suspected in 5 patients. Of these, 2 showed a demonstrable leak from the caecostomy site: 1 died from septicaemia, but the other was salvaged. Of the other 3 non-demonstrable urinary leak patients, 1 had prolonged adynamic ileus which resolved with conservative treatment, 1 had acute intestinal obstruction and 1 had a burst abdomen; the latter 2 required surgical correction in the form of lysis of adhesions and resuturing of the burst abdomen respectively. All 5 patients with demonstrable and non-demonstrable urinary leaks (2 of them had received pre-operative radiation therapy) belonged to the standard CUR group. Minor wound infection was present in 1 patient each from both the standard CUR and modified CUR groups. In addition, fever with urinary tract infection (2 patients) and hyperchloraemic acidosis corrected by sodium bicarbonate therapy (1 patient) occurred in the standard CUR patients. The mean post-operative stay was 25 days for the standard CUR and 21 days for the modified CUR groups. Post-operative urograms (Table 2) were done at 6 weeks and 3 months and were available in 28 patients, showing preservation of normal upper tracts in 19 patients (38 units), improvement in previously dilated tracts in 6 patients (8 units) and worsening of upper tracts in 3 patients (4 units). Reflux was noted in 3 patients (pre-operatively normal upper tracts)—on the left side in 2 and on both sides in 1. Of the 3 patients who developed worsening of the upper tracts, 1 developed bilateral renal failure due to para-aortic node mass leading to death at 24 months, and the other 2 had hydronephrosis due to reflux in 1 and ureterocolonic anastomotic stenosis in the other—both were lost to follow-up after 12 months.

Continence

Continence was assessed 3 months after surgery and data were available on 28 patients (Table 3). Complete continence with no leakage between catheterisations and dry nights was achieved in 23/28 patients (82%). Of the remaining 5 patients, 4 had partial continence, implying leakage only at night and occasional leakage between catheterisations, and 1 was totally incontinent, requiring a

Table 2 Upper Tract Status

	No of patients	*No. of renal units*
Pre-operative (n = 30)		
Normal	22	44
Unilateral hydronephrosis	4	4 (n = 4)
Bilateral hydronephrosis	4	8
Post-operative (at 3 months) (n = 28)		
Normal	19	38
Improvement in previously hydronephrotic tracts	6	8 (n = 4)
Worsening	3	4 (n = 2)
Unilateral	2	2
Bilateral	1	2
Reflux		
No reflux	25	50
Unilateral	2	2 (n = 2)
Bilateral	1	2

Table 3 Results of Continent Urinary Reservoirs

Continence	
Complete	25* (89.2%)
Partial	2 (7%)
Failures	1 (3%)
Not evaluable	2
Pouch capacity (ml)	
350–650	25
250–350	2
<250	1

N = 30, evaluable = 28 (1 died post-operatively and 1 was lost to follow-up).
Follow-up 6–48 months (median 24 months).
* 2 had revision surgery and are continent at 6-monthly follow-up

collection bag continuously. The pouch capacity was 350–650 ml in 25 patients, 250–350 ml in 2 and less than 250 ml in 1. A revised continence procedure was done in 2 patients and both are completely continent 6 months later. The remaining 3 patients refused revision surgery; 25/28 patients are completely continent after a follow-up of 6–48 months, giving a success rate of 89%.

Discussion

We have been performing ileal conduits as the sole urinary diversion after cystectomy for the past 10 years, with a delayed complications rate of 12% in more than 100 cystectomies. However, in keeping with the modern trend, we decided to undertake continent urinary diversion procedures from January 1987. Since then we have constructed continent urinary reservoirs using an ileocolonic segment in 30 patients. In the initial period, we restricted these procedures to patients with only limited muscle-infiltrating tumours (B1 or B2) of the bladder without pre-operative radiation therapy or chemotherapy. However, this procedure is now being done for patients with stage B2–C bladder tumours with or without pre-operative therapy.

The modification of the operative technique was aimed at reducing the problem of urinary leak which occurred in 2 patients and was suspected in another 3. Four of these 5 patients had re-operations, at which time the pouch suture lines and ureterocolonic anastomosis were found to be intact. This led us to believe that the leaks were occurring from the caecostomy site (in 2 patients the caecostomy catheter had slipped out of the caecum). Hence we modified our technique as described earlier. The most important modification was the use of a 0.5 cm appendicular stump for caecostomy catheter placement, which completely eliminated the caecostomy leaks in the last 10 patients. We feel that the purse-string suture on the appendicular stump fits snugly to the catheter and prevents the caecostomy catheter from slipping, thereby obviating the need for further retroperitonealisation of the caecostomy. The incision on the anterior taenia for detubularisation of the colon has reduced the blood loss to some extent since the taenia is relatively avascular, though we believe that the blood loss is more related to cystectomy than to the diversion procedure. The "pull-through" technique of delivery of the ureters into the colonic cavity has increased the ease of anastomosis and has, to some extent, helped to reduce the operative time.

Another problem was that of prolonged non-obstructive ileus which, we believe, occurred because of a non-demonstrable urinary leak from either the caecostomy site or the pouch suture line and needed effective gastrointestinal decompression and intravenous hyperalimentation. Similar problems have been reported by others (Ahlering *et al*., 1989; Chin and Ferguson, 1989). Wound infections and symptomatic urinary tract infections have not been a major problem in the present series. One patient who developed hyperchloraemic acidosis confessed to irregular and delayed self-catheterisation with inter-catheterisation periods extending to 8 h. The correction of this default soon restored the patient's normal metabolic status.

Patients with continent urinary reservoirs, in the initial operations, required longer hospitalisation than those with an ileal conduit because we were in the process of standardising the procedure. Lately, however, the hospital stay has been reduced to 12–15 days, which is almost the same as after the ileal conduit operation.

The status of the upper tracts was evaluated 3 months after surgery and showed preservation of normal function in 19 patients (38 renal units) and improvement in 6 (8 renal units), indicating the safety of the procedure. The pouchograms showed reflux in 3 patients, which was considered to be due to technical failure; however, 1 patient with bilateral reflux maintained normal upper tracts because she was totally incontinent. The deterioration rate of renal units in our series, 4/60 units (6.5%), was significantly less than the 12–15% with ileal conduits reported in the literature, though it is conceded that our follow-up is short. Complete detubularisation of the colon reduces the pressure within the pouch and this, combined with a non-refluxing ureterocolonic anastomosis, either tunnelled (Rowland *et al*., 1985) or the open Goodwin type (Goodwin *et al*., 1953), helps to preserve the function of the upper tracts. In 4 patients urinary tract infection, confirmed by positive urine cultures for Gram-negative bacteria, was probably due to prior urinary infection or to inadequate sterilisation of the colonic bacterial flora. This complication was also reported by Ahlering *et al*. (1989).

Our success rate of complete continence in 25 patients (89%) appears satisfactory, and the failure in the remaining patients could be attributed to technical faults in our initial patients. Only Ahlering *et al*. (1989) reported 100% continence rate with CURs in a series with no re-operations. As far as pouch capacity is concerned, we had excellent results in 25 patients (capacity 350–650 ml) who are completely continent. We also believe that the pouch capacity of less than 300 ml must have partly contributed to the failure of continence.

In conclusion, we feel that continent urinary reservoirs are more acceptable to patients, though they have to accept a stoma over the abdominal wall. It can be covered with gauze, giving a better aesthetic appearance. However, it requires intermittent self-catheterisation, giving a sense of intermittent evacuation. It is our firm belief that the continent urinary reservoir (Indiana pouch) procedure is a better alternative for developing countries because it is economically more suitable. The complications are mainly related to the cystectomy itself and those related to the diversion procedure are comparable to those with ileal conduits (Ahlering *et al.*, 1989) or with other colonic conduits (Husmann *et al.*, 1989). With our modified technique we hope to achieve better results in terms of continence and reduced complications.

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Cystodiathermy under Local Anaesthesia using the Flexible Cystoscope

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Summary—The use of the flexible cystoscope in the follow-up of patients with bladder carcinoma is becoming more widespread. In a series of 17 patients, cystodiathermy of small recurrent tumours using the flexible cystoscope and topical urethral anaesthesia proved to be a safe, effective and well tolerated procedure.

Out-patient flexible cystourethroscopy, as a method for surveying bladder carcinoma, has now become routine in most centres (Kahn, 1987). Approximately 5 to 10% of patients undergoing cystoscopy will have recurrences that are small in size and few in number. This study was designed to investigate the possibility of treating these recurrences by cystodiathermy using the flexible cystoscope and topical urethral anaesthesia. Over a period of 6 months, 17 patients were recruited into this pilot study from a total of just over 200 patients undergoing flexible cystoscopy.

Patients and Methods

Patients were assessed by preliminary cystourethroscopy to determine the size, number and location of recurrent bladder tumours. Recurrences > 1 cm in diameter (or approximately 5 times the width of the diathermy electrode) were considered unsuitable for treatment under local anaesthesia and were treated under general anaesthesia using the rigid cystoscope.

The technique of flexible cystoscopy was similar to that described by Fowler (1984). We used the Olympus CHF P10 choledochofiberscope, which incorporates a 2 mm irrigation/instrument channel, a range of tip-bending of 160° upwards and 130° downwards and a working length of 330 mm. The coagulating electrode was 4 F (Order number 27023 T; Storz) and was used with a high frequency cord (Order number 27170). The Eschmann TD311 Series 2(GB), a solid state electrosurgical unit, was set for monopolar coagulation at 3.5 (*i.e.* half maximum power output rated at 7 or 125 W). An earthing plate electrode was strapped to the patient's thigh and glycine was used as the irrigating fluid.

A mid-stream specimen of urine (MSU) was obtained from all patients pre-operatively, and 4 days after the cystoscopy. Tolerance was graded subjectively on a scale of 1 to 4 (Table 1). Post-operative symptoms and the patient's general impression of the procedure were obtained by means of a telephone conversation with the patient 1 week after cystodiathermy. The follow-up period after initial cystodiathermy was 12 months. An initial follow-up cystoscopy was performed at 3 months and thereafter as necessary.

Results

Seventeen patients (13 male, 4 female) were studied. Their ages ranged from 39 to 93 years (median 69). A total of 58 recurrent tumours (range 1–8, average 3.4) were treated by diathermy at initial cystoscopy and the average duration of the procedure was 25 min (range 10–45). Cystodiathermy was performed using topical urethral anaesthesia alone and no additional analgesia.

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Table 1 Summary of Patients Treated by Flexible Cystoscopy

No. of patients	*Sex*	*No. of lesions treated*	*Duration (min)*	*Patient tolerance**	*Initial follow-up cystoscopy (Anaesthesia)*
1	M	1	20	2	Clear
2	F	1	20	1	Clear
3	M	1	15	1	Clear
4	F	3	20	1	1 recurrence (Local)
5	M	6	35	1	Recurrences (General)
6	M	1	10	1	Clear
7	M	3	35	3	Clear
8	F	5	25	1	Clear
9	M	3	15	1	2 recurrences (Local)
10	M	8	45	3	Recurrences (General)
11	M	7	30	2	Recurrences (General)
12	M	6	35	2	Recurrences (General)
13	M	2	25	2	2 recurrences (Local)
14	M	3	30	1	5 recurrences (Local)
15	M	1	20	1	3 recurrences (Local)
16	M	6	40	2	5 recurrences (Local)
17	F	1	15	1	Clear

*Grading for patient tolerance

Comfortable	1	Painful	3
Uncomfortable	2	Unbearable	4

Tolerance of the procedure was graded subjectively on a scale of 1 to 4 (Table 1); 10 patients described it as comfortable, 5 as uncomfortable and 2 as painful. Of the 2 patients who found the procedure painful, the first had required preliminary urethral dilatation and the other had received cystodiathermy to a recurrence situated at the bladder neck. Poor tolerance scores were not related to the age of the patient, but seemed to correlate well with the longer duration of the procedure (average 33 min) and with the diathermy of a larger number of recurrences (average 4.7). All 4 women described the procedure as comfortable, indicating perhaps a better tolerance by women than men.

No urinary tract infection resulted *de novo* from this procedure. The post-operative symptoms ranged from mild dysuria of 24 hours' duration to the passage of blood clots and marked urinary frequency for 4 days. With one exception, patients felt that the post-operative symptoms following flexible cystoscopy were less severe than those following rigid cystoscopy. We feel that the larger calibre of the rigid cystoscope may be more traumatic to the urethra and so account for this observation.

Seven patients were clear at their first follow-up cystoscopy, 6 had recurrent disease which was suitable for further treatment under local anaesthesia, but 4 patients required general anaesthesia for the treatment of recurrences that were either greater than 1 cm in diameter or more than 8 in number. The longer period of follow-up showed that patients with more than 5 recurrences at their initial cystoscopy would usually go on to develop recurrences that were unsuitable for treatment by local anaesthetic procedures alone. In contrast, the 12 patients with up to 5 recurrences at presentation required a total of 33 follow-up cystoscopies over 12 months, of which 15 were clear and only 6 required procedures under general anaesthesia (Table 2).

Discussion

Day-case flexible cystoscopy under local anaesthesia has been shown to be a safe, fast and cost-effective means of surveillance of bladder carcinoma (Fowler *et al.*, 1984; Webb *et al.*, 1984; Kahn, 1987). The procedure avoids the risk of repeated general anaesthesia in a population of patients at risk from age-related cardiac and respiratory disorders. Patients have also expressed a preference for this form of out-patient surveillance of their bladder carcinoma.

This pilot study has demonstrated the technique of flexible cystodiathermy to be successful and acceptable in the treatment of recurrent superficial bladder tumours. Although the largest number of

Table 2 Follow-up Cystoscopies over a 12-month Period

No. of recurrences at presentation	*No. of cystoscopies*	*Clear*	*Recurrences treated under*	
			Local anaesthesia	*General anaesthesia*
≤5 (n = 12)	33	15	12	6
>5 (n = 5)	19	1	3	10

recurrences treated in 1 session in this study was 8, there is no absolute limit, and there is no reason why multiple small recurrences should not be treated in 2 or more sessions. Cystodiathermy to most areas of the bladder was well tolerated; treatment of recurrences in the trigone or bladder neck was painful, but may be better tolerated if a local anaesthetic were to be injected directly into the site. A limitation of flexible cystodiathermy is the size of the diathermy electrode, which precludes the treatment of larger recurrences. However, larger bladder tumours have been successfully resected under local anaesthesia using a rigid cystoscope and prior injection of lignocaine into the planned site for resection (Engberg *et al.*, 1983).

We have co-ordinated the timing of the flexible cystoscopy list with the urology out-patient clinic and are therefore able to offer diagnostic cystoscopy to some patients at the time of their original clinic visit. This has resulted in a reduction in the time interval between presentation and diagnosis.

Practical applications for the flexible cystoscope such as biopsy, retrograde pyelography (Reddy and Hulbert, 1986), retrieval of ureteric stents (Fowler, 1987) and aiding the difficult male catheterisation (Krikler, 1989) have been described. We have found cystodiathermy to be a further useful application when dealing with small recurrences of bladder carcinoma.

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Hormonal Cytoreduction and Radiotherapy for Carcinoma of the Prostate

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Summary—We report the effect on prostatic volume of the administration of the luteinising hormone-releasing hormone (LHRH) analogue goserelin in 22 patients with locally advanced carcinoma of the prostate; 20 achieved a significant reduction in volume, the median volume being 66 ml before treatment (range 40–130) and 30 ml after 17 weeks (range 13–47). If used before external beam radiotherapy (RT), volume reduction will permit smaller boost fields and thus potentially reduce adverse radiotherapy effects. In addition, reducing tumour volume before RT may lead to an increase in local control. We discuss the possible role of hormonal volume reduction in the management of prostatic cancer.

External beam radiotherapy achieves long-term local control of the majority of prostate cancers (Bagshaw *et al.*, 1985), but acute radiation reactions affect bowel in 79% and bladder in 65% of patients (Sack *et al.*, 1987). Severe late side effects (intractable or requiring surgical correction) occur in 5 to 16% of patients (Hanks, 1985). Dewit *et al.* (1983) found that intestinal radiation injury correlated with increasing dose (>65Gy) and the length of rectum (>10 cm) included in the target volume. Other authors have documented an increased incidence of complications with boost field size >150 cm^2 (Rosen *et al.*, 1985) and prostatic dose >70Gy (Hanks *et al.*, 1985).

Hormonal therapy with reversible androgen deprivation allows reduction of tumour volume and hence the size of the radiotherapy field. Hormonal cytoreduction before RT was first reported by Green *et al.* (1984) and in a small group of patients tumour control appeared better than expected. A Radiotherapy Oncology Group study (Pilepich *et al.*, 1987) showed a low recurrence rate in patients treated with stilboestrol or megestrol before and during RT. Neither of these studies commented on alteration in RT volumes or possible advantages in reduced morbidity.

A combination of hormonal cytoreduction and RT might produce benefits in 3 ways:

1. Reduce normal tissue in RT target volume, leading to an improvement in acute and late irradiation reactions.
2. Favourably modify the dose/control relationship by reducing tumour volume before irradiation.
3. Permit dose escalation for equivalent normal tissue damage.

We have therefore undertaken a study of hormonal cytoreduction using the LHRH analogue goserelin before and during radiotherapy for locally advanced (T3) carcinoma of the prostate to document the timing and extent of reduction in prostate volume following androgen deprivation.

Patients and Methods

The study group comprised 22 patients with locally advanced carcinoma of the prostate. Their characteristics and tumour category and grade are shown in Table 1. Histological diagnosis was obtained from tissue obtained at transurethral resection (TUR) in 10 patients and needle biopsy in 12. Gleason scores were calculated in the TUR patients but not in the needle biopsies.

Read at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, June 1990

Table 1 Details of Patients. Tumour Category and Grade

Category (n = 22)	T	T3	T4	
		20	2	
	N	N0	N1–3	
		17	5	
	M	M0	M1	
		19	3	
Grade (n = 22)	G1	G2	G3	
	1	13	8	
Gleason grade (n = 10)	4	6	7	8
	1	3	5	1

Before entry into the trial all patients underwent radio-isotopic bone scintigraphy, measurement of serum markers and ultrasonic measurement of prostatic volume. Pelvic nodal status was assessed by computed tomography (CT) scan.

Prostatic volume was measured every 4 weeks with a Bruel and Kjaer type 1846 scanner fitted with a type 1850 rectal probe and a 4mHz rectal transducer type 8531. Surface area measurements of the prostate image were calculated by encircling the image with a light pen and volumes were calculated by measuring serial steps at 0.5 cm intervals using the formula shown in Table 2. The accuracy and reproducibility of the technique was assessed by 2 observers independently measuring prostatic volumes. Serum markers were measured monthly. CT scans for radiotherapy planning were done before hormone therapy, and again when prostatic volume had stabilised on ultrasound measurement.

Androgen deprivation was by administration of goserelin depot 3.6 mg at 4-weekly intervals. To avoid the possibility of tumour flare after the first injection, this was preceded by 1 week's treatment with cyproterone acetate (CPA). CPA was continued for 3 weeks. Radiotherapy commenced when the prostatic volume stabilised (2 measurements 4 weeks apart within 10%). Goserelin was continued until the end of radiotherapy. The 3 patients with M1 disease were included for the purposes of documenting volume reduction. They did not go on to radiotherapy, and LHRH analogue treatment was continued.

Table 2 Formula for Calculating Prostatic Volume

Planimetric volume measurement
Surface area measured at 0.5 cm intervals

$$V_1 = \frac{L^2}{4} \times T \times 0.7$$

$$V = V_1 + V_2 + V_3 + \ldots\ldots V_n$$

Where V = volume (ml), L = perimeter (cm) and T = slice (cm)
90–95% accurate

Radiotherapy was given in 2 phases. The phase I treatment volume included all initial disease including seminal vesicles and, in CT node negative patients, the lower pelvic lymph nodes. In node positive patients the Phase I volume included the whole pelvis. After giving 50 Gy, the volume was reduced to include residual abnormalities only, to a total dose of 64 Gy in 6.5 weeks. All treatment volumes were localised using CT and 2 Gy daily treatments were given using 6–8 MeV linear accelerators.

Results

Twenty of the 22 patients showed a significant reduction in prostatic volume. Median volumes are shown in Table 3 and volume reduction expressed as a percentage of pre-treatment volume in the Figure. Prostatic volumes stabilised at 3 to 5 months (median 3.5).

One patient showed no reduction in volume and in another patient with a T4 tumour, diffuse invasion of periprostatic tissue meant that we were not confident of the accuracy of our volume measurements. Both of these patients commenced irradiation at 2 months.

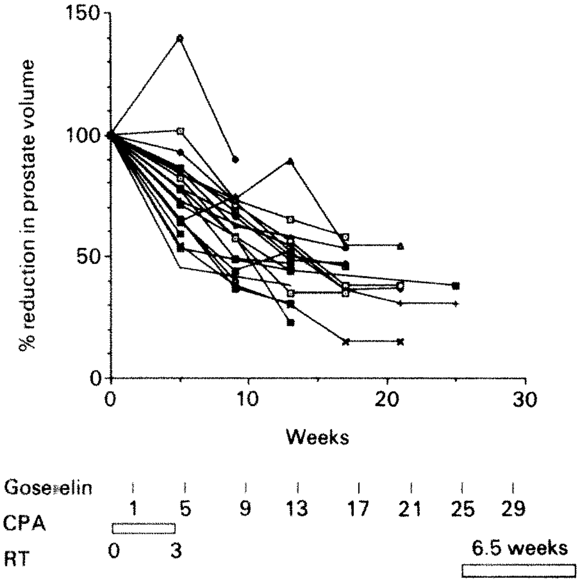

Fig. Percentage reduction in prostatic volume after androgen deprivation.

Table 3 Prostatic Volume during Administration of LHRH Analogue

	Volume (ml)	
Week no.	*Median*	*Range*
0	66	40–130
5	47	30–94
9	35	17–57
13	39	17–70
17	30	13–47

Serial prostatic specific antigen assays were available in 16 patients. In 13 cases PSA fell to <10 ng/ml (to <4 ng/ml in 10). In one patient PSA did not fall with goserelin in spite of an 80% reduction in volume but after RT his PSA became <4 ng/ml. In 2 other patients there was no fall in PSA. Both had high levels on entry (60 and 55 ng/ml) and have subsequently developed metastases.

Changes in serum prostatic acid phosphatase (PAP) levels did not reflect the changes in prostatic volume.

There were no major untoward events attributable to treatment. A number of patients complained of hot flushes. One patient developed a vesico-colic fistula (outside the radiotherapy fields) from pre-existing diverticular disease 4 months after radiotherapy.

Discussion

Optimal radiotherapy for prostatic cancer balances the probability of gaining local control against the chance of producing irradiation-induced normal tissue damage. Treatment factors related to increasing control may include field size and dose. Although large field size has not been demonstrated to produce disease-free or survival advantages (Rosen *et al.*, 1985; Asbell *et al.*, 1987), boost fields of less than 8 cm dimension (Rosen *et al.*, 1985) or periprostatic doses measured 4 cm from the midline of <55Gy (Hanks *et al.*, 1985) have been implicated in an increased incidence of local failures in T2/3 tumours. The establishment of a dose-control relationship for carcinoma of the prostate is controversial but Hanks *et al.* (1985, 1987) suggested an optimal dosage of 60 Gy for stage A lesions rising to 70 Gy for stage C tumours, the higher dosage producing an 11% control advantage.

The current doses used are at the beginning of the steep part of the dose-complication curve and dose escalation to improve local control for larger tumours is not feasible with existing external beam radiotherapy methods. CT planning improves tumour localisation and allows individualisation of field size.

Our results show that hormonal reduction of prostatic volume is consistently achieved in the majority of patients and permits modification of CT-planned irradiation fields. Median time to stabilisation of prostate volume was 3.5 months, but because over 50% of our patients needed more than the 3 months suggested by Beacock *et al.* (1987) to reach maximum volume reduction, sequential ultrasound measurements are necessary for optimal individualisation of treatment.

Those patients who had obstructive urinary symptoms before starting treatment improved symptomatically while on goserelin. Many urologists are wary of treating symptomatic patients with RT because of the fear that oedema of the prostate during treatment may lead to retention and therefore it is common practice to treat such patients by transurethral prostatic resection (TURP) before RT. There is some inconclusive evidence that TURP in M0 patients accelerates the development of metastases (Sandler and Hanks, 1988); by reducing the necessity for surgery, hormonal cytoreduction may delay the onset of metastatic disease.

There are 3 theoretical disadvantages to this approach to the treatment of locally advanced prostatic cancer. Firstly, RT is most effective against dividing cells and androgen deprivation increases the proportion of cells in the G0 phase which are relatively radio-resistant. However, there is no clinical evidence that this is a problem in conventionally fractioned RT schedules (Withers *et al.*, 1989). An analogy can be made with breast cancer patients. The randomised studies of patients treated with conservative surgery, local radiotherapy and adjuvant hormone therapy with tamoxifen show that combined treatment with hormones and RT improves local control (Rubens *et al.*, 1989).

Secondly, although the identifiable tumour volume may be reduced by androgen deprivation, it is possible that viable tumour cells remain in the periprostatic tissues which are now not included in the high dose boost field. They are, however, included in the Phase I pelvic field and this dose should be enough to "sterilise" microscopic disease (Fletcher, 1983).

Thirdly, hormone-sensitive cells may be "desensitised" by this approach and subsequent relapse may therefore not be responsive to renewed androgen deprivation. It is too early in the natural history of our patients for us to be dogmatic, but of the 5 patients who have developed metastases so far, 4 showed biochemical evidence of hormone resistance during their initial treatment, developing rising levels of PSA and/or PAP while still on goserelin. They have not responded satisfactorily to the reintroduction of androgen deprivation. The fifth patient, who responded well to initial treatment, also responded to the reintroduction of goserelin 8 months after radiotherapy.

Our results are sufficiently encouraging for us to consider that this treatment is worthy of further study.

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Natural History and Prognosis of Prostate Carcinoma in Adolescents and Men under 35 Years of Age

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Summary—Prostate cancer is extremely rare in men under 35 years of age. The tumour is invariably poorly differentiated and aggressive, with rapidly growing bulky soft tissue metastases and negative tumour markers. Bone metastases develop late and are usually osteolytic. The disease responds poorly to radiation or hormonal therapy and is too advanced at presentation for radical surgery. Chemotherapy appears to be of some benefit, though in the majority of cases death occurs within a year.

We describe a 31-year-old man with carcinoma of the prostate. A review of the literature is presented. This is the first patient in whom the epithelial origin of the prostate cancer was confirmed by immunoperoxidase staining with prostatic specific antigen. Plasma prostatic specific antigen was normal despite a large tumour burden and widespread metastases. He did not respond to conventional treatment.

The phenotypic expression and biological behaviour of these tumours are distinct from those occurring in men beyond the fourth decade.

Within the heterogeneous pool of prostate cancer less than 1% of patients are under 40 years of age. Carcinoma of the prostate is extremely rare in men under 35 years of age and needs to be distinguished from sarcoma of the prostate. We present the case of a 31-year-old man with carcinoma of the prostate with normal tumour markers; 25 other patients described in the world literature are reviewed. Together they represent a homogeneous group of a virulent clone which is poorly differentiated with large soft tissue tumour burden resistant to treatment and poor survival.

Case Report

A 31-year-old man presented in October 1989 with haematuria and clot retention. Rectal examination revealed a large irregular malignant prostate gland. Following bladder washout an intravenous urogram demonstrated an extensive irregular mass in the bladder (Fig. 1) with a partially obstructed right

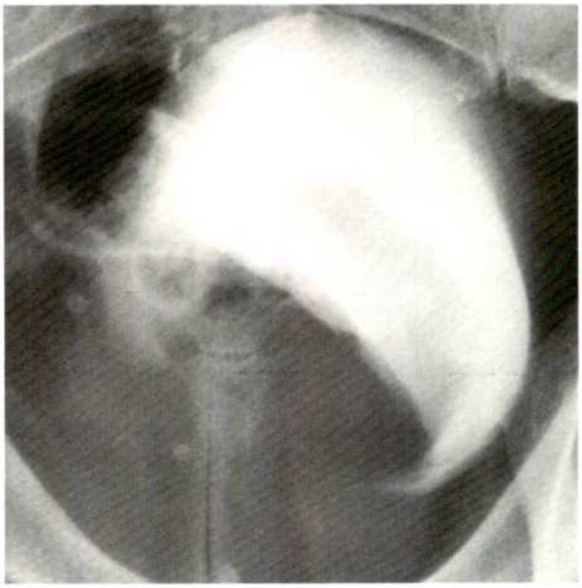

Fig. 1 Intravenous urogram showing large filling defect in the bladder

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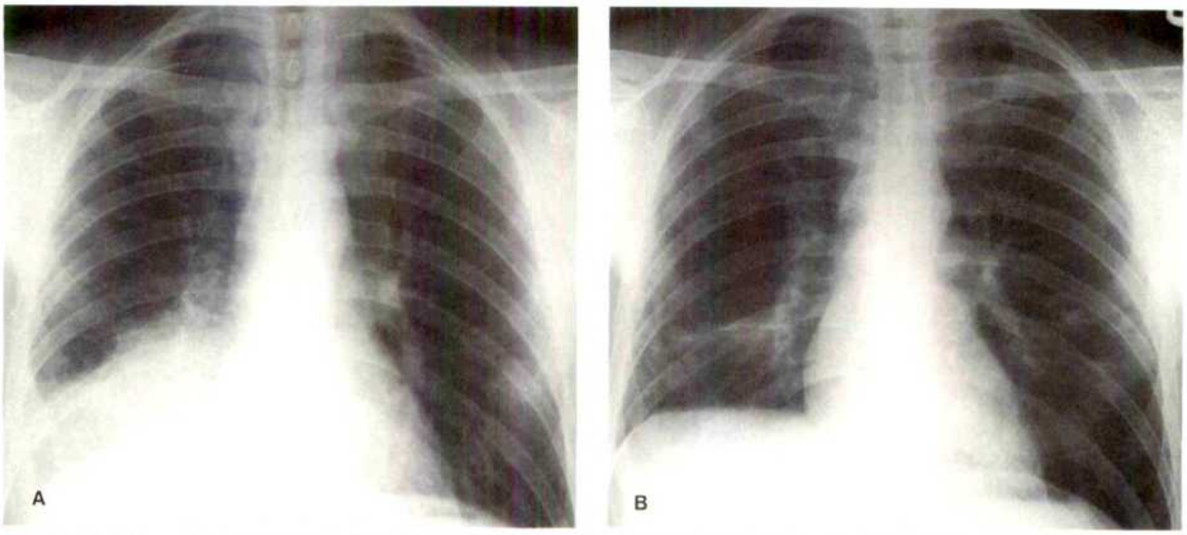

Fig. 2 (A) Chest X-ray at presentation with extensive right lower zone metastases. (B) Almost complete resolution of chest metastases 2 months after chemotherapy.

kidney. Serum urea, creatinine, electrolytes, alpha fetaprotein and beta human chorionic gonadotrophin were in the normal range. Serum prostatic acid phosphatase (PAP) was normal (0.73 iu/l; normal reference range up to 1 iu/l). Prostatic specific antigen (PSA) at 1.8 ng/ml was within the Hybritech normal range of 4 ng/ml. Chest X-ray (Fig. 2a) revealed a large mass in the right lower zone. Histology of the transurethrally resected specimens of prostate showed extensive infiltration by undifferentiated prostatic carcinoma (Fig. 3). Immunoperoxidase studies showed weak positive staining with prostatic specific antigen confirming this to be an epithelial malignancy rather than a sarcoma.

Computed tomography (CT) demonstrated extensive pelvic spread from a large prostate primary compressing the bladder (Fig. 4A), with enlarged internal and common iliac lymph nodes. Despite large tumour burden with extensive soft tissue disease there was no uptake on bone scintigraphy to indicate skeletal metastases.

The patient underwent bilateral subcapsular orchiectomy with no symptomatic improvement. In view of his young age and aggressive nature of the disease, a month later he was commenced on 4 cyclical courses of chemotherapy. This consisted of intravenous vincristine, adriamycin, ifosphamide and Ondansetron for control of nausea. Initial response to this combined treatment was dramatic, with almost complete resolution of chest metastases (Fig. 2B) and pelvic disease (Fig. 4B). Five months after presentation he remained well and had reached a plateau phase in his response to chemotherapy. Residual pelvic symptoms of tenesmus were treated with palliative irradiation.

Two months later the patient progressed with bilateral lung metastases and lytic deposits in his cervical spine. The latter were treated with palliative radiotherapy. He continued to deteriorate, developed widespread metastases and died 8 months after presentation.

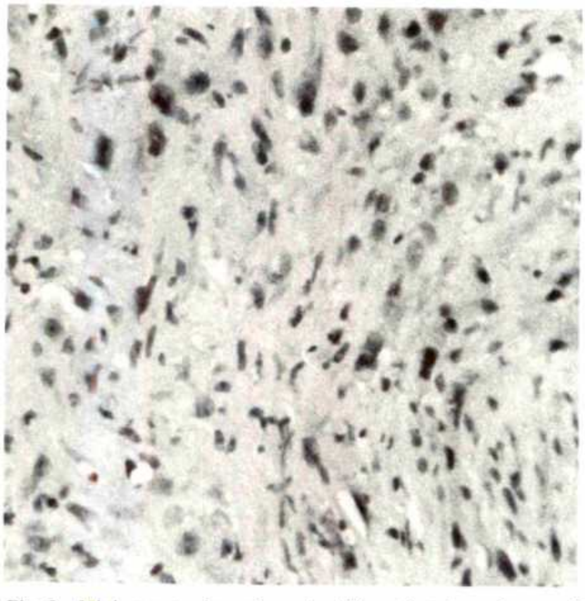

Fig. 3 High power view of poorly differentiated carcinoma of the prostate.

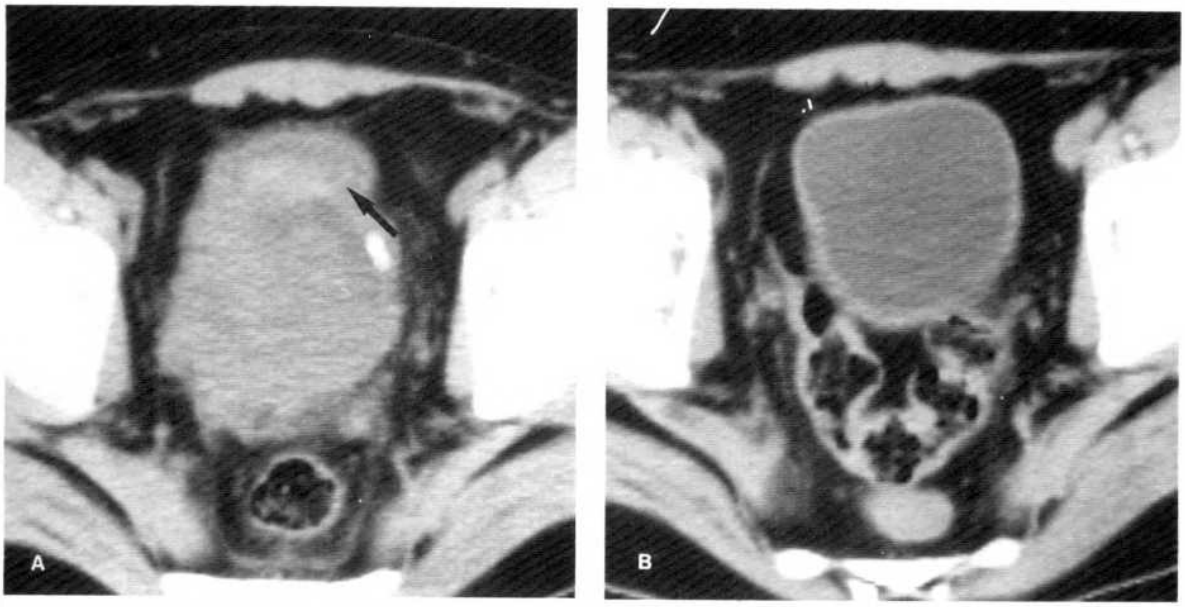

Fig. 4 (A) CT scan of the pelvis demonstrating extensive prostate tumour occupying most of the pelvis and compressing the bladder (arrowed). (B) Identical CT cut of the pelvis 2 months after chemotherapy with considerable resolution of pelvic disease and bladder no longer compressed.

Discussion

Carcinoma of the prostate is a condition primarily found in older men with a median age of 70 years (Kagan and Fox, 1959; Murphy *et al.*, 1982). It is rare in men less than 50 years of age, with an incidence of 0.8 to 1.1% (Tjaden *et al.*, 1965; Huben *et al.*, 1982). Under the age of 40 years the incidence is 0.07% (Immergut and Flocks, 1966). Sarcoma is the most common malignant disease of the prostate in children and young adults (Raney *et al.*, 1986). However, adenocarcinoma of the prostate is extremely rare, with only 25 previous reports (Table). Seven of these patients were children under 14 years of age; there were 7 adolescents under 18 years and 11 other patients within their third decade of life.

The clinical picture and biological behaviour of these tumours, typified in our patient, are quite distinct from those of carcinoma of the prostate in men beyond the fourth decade. The usual presentation is urinary retention and haematuria with a large tumour burden. The carcinoma is poorly differentiated, with negative serum PAP and PSA (Shimada *et al.*, 1980; Briet *et al.*, 1986; Culkin *et al.*, 1986). Tumour tissue acid phosphatase has also been reported to be in the normal range (Suzuki, 1953; Kagan and Fox, 1959). The regional and distant lymph nodes are usual sites of metastases; more strikingly, soft tissue disease and in particular lung metastases are common (12 previous reports) (Table). Unlike conventional carcinoma of the prostate, bone metastases develop late and are usually osteolytic rather than osteoblastic (Chiu and Weber, 1974; Shimada *et al.*, 1980). Furthermore, skeletal resistance to tumour seeding with large lymph node response is a favourable prognostic sign in patients with metastatic disease (Sandhu *et al.*, 1990). In this series of 26 patients, 21 had autopsies performed or were investigated for the presence of bone metastases. Ten patients had proven bone metastases prior to death and in the majority these developed late and were osteolytic. In 11 patients, despite large tumour burden and lymph node involvement, an apparent resistance to skeletal metastases (MO disease) conferred no advantage; the time to progression was short, since the natural history is aggressive. The outlook is very poor, and with 3 exceptions, all patients were dead within 15 months (Table). This compares poorly with the recognised 50% 2-year survival rate of adults with bone metastases (George, 1988).

The clinical characteristics of prostate cancer in these rare cases support the view of a distinct cell type which is highly virulent and responds poorly to hormonal or radiation therapy. The disease is invariably too advanced at presentation for radical surgery. Unlike conventional adenocarcinoma,

Table Details of Patients

Author(s)	*Year*	*Age of patient (years)*	*SAP level*	*Lung/bone metastases*	*Survival (months)*	*Treatment*
Gardner and Cummins	1912	17			5	
Aleksejew and Dunajewsky	1930	20 months		None	6	
Spath	1936	3		No autopsy	3	
Arimitsu	1939	13		Lung and bone	72	
Nicholson	1945	15		No autopsy	3.5	
Kimbrough and Lewis	1952	20	Normal	Lung and bone	6	Orchiectomy and DXT
Kimbrough and Lewis	1952	17	Normal	Lung	12	Orchiectomy and DXT
Suzuki	1953	16	Normal	Lung	7	DXT
Hunata	1956	20 months	Normal	Pleura	1	
Kagan and Fox	1959	3	Normal	Lung	7.5	Radical prostato-cystectomy, DXT
Reiss and Thierbach	1964	16	Normal	Lung and bone	3.5	Orchiectomy
Ellner *et al.*	1965	17		Lung and bone	10	Orchiectomy
Immergut and Flocks	1966	18	Normal	Pleura and bone	7	Radical prostatectomy, partial Cystectomy, DXT
Koenig and De Villiers	1968	9		Lung	6	DXT, surgery
Byar and Mostofi	1969	20			31*	
Byar and Mostofi	1969	30			13	DXT, chemotherapy
Hansen and MacMeekin	1974	25		Discovered at autopsy		
Hansen and MacMeekin	1974	33		Discovered at autopsy		
Elliott *et al.*	1977	24		Discovered at autopsy		
Shimada *et al.*	1980	12	Normal	Lung and bone	15	Chemotherapy
Weitzner *et al.*	1980	27		Lung and bone	13	Orchiectomy, DXT, chemotherapy
Petit *et al.*	1981	16		Bone	2	Oestrogens, DXT
Petit *et al.*	1981	27			1	Oestrogens, DXT
Culkin *et al.*	1986	25	Normal	Bone	6	Orchiectomy
Briet *et al.*	1986	20	Normal		60*	Oestrogens, DXT, chemotherapy
Sandhu *et al.* (present study)	1991	31	Normal, including PSA	Lung and bone	8	Orchiectomy, DXT, chemotherapy

*These patients were alive at the time of publication.

chemotherapy appears to be of some benefit. Shimada *et al.* (1980) raised the possibility of the tumour arising from basal cells of the prostate. The basal cells are considered to be located between the columnar cells and the basement membrane in both ductal and glandular portions of the prostate. Acid phosphatase activity is said to be absent in their cytoplasm. Low acid phosphatase activity may be related to the basal cell origin of this malignancy. The reason for PSA being in the normal range is not clear, since the level of circulating PSA is directly proportional to prostatic volume and grade (Stamey and Kabalin, 1989; Stamey *et al.*, 1989). The basal cell origin may account for the PSA value of 1.8 ng/ml, but it is worth noting that in a series of 265 patients with stage D prostate cancer 12% had a PSA value in the normal range (Myrtle *et al.*, 1986).

This case emphasises the heterogeneity of prostate cancer and the need to be aware, in young men, of highly anaplastic carcinoma of the prostate with negative tumour markers and atypical spread, necessitating early diagnosis and treatment. Unlike standard adenocarcinoma, there is some response to chemotherapy.

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Spinal Cord Compression in Prostate Cancer. A 10-year Experience

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Summary—Of 478 patients treated at a single institution for prostate cancer, 29 developed spinal cord or cauda equina compression. In 5 patients, spinal cord compression was the first evidence of malignancy. Clinical features were predominantly pain, weakness, sensory and sphincter disturbance. The median duration of symptoms was 2 weeks, although the diagnosis was made rapidly at presentation. Clinical diagnosis correlated well with myelographic findings. Only 1 patient suffered neurological deterioration as a consequence of myelography. The functional outcome was dependent on the ability to walk prior to treatment. The median survival in those who were bed-ridden following treatment was 6 weeks (range 3.5–13) and 21 weeks (range 7–110+) in those who were ambulant following therapy.

Compression of the spinal cord and cauda equina is an important complication of metastatic malignancy and its frequency in patients with any malignancy is 5 to 10% (Barron *et al.*, 1959; Gilbert *et al.*, 1978). Although it is not widely recognised, prostate cancer is the second most common cause of spinal cord compression in men (Veith and Odom, 1965; Constans *et al.*, 1983).

The incidence of spinal cord compression in patients with prostate cancer has been estimated at between 1 and 12% (Rubin *et al.*, 1974; Gilbert *et al.*, 1978; Constans *et al.*, 1983; Kuban *et al.*, 1986; Liskow *et al.*, 1986). The aims of treatment are to preserve or restore neurological function and to relieve pain. Prevention or early recognition of this complication is important, since recovery of function is related to the degree of neurological deficit prior to treatment (Wright, 1963; White *et al.*, 1971; Findlay, 1984; Iacovou *et al.*, 1985; Latini *et al.*, 1989).

We have performed a retrospective analysis of this condition by reviewing the records of patients with prostate cancer seen at this institution between 1979 and 1988, allowing a minimum follow-up of 1 year.

Patients and Methods

The records of 478 patients with prostate cancer were reviewed. All patients had histological evidence of carcinoma of the prostate with no other malignancy present. The Urological Cancer Research Unit has a national referral pattern in addition to secondary and tertiary referrals within New South Wales. Thus the population sample has been biased by an increased proportion of patients who have previously been treated by hormonal manipulation, radiotherapy and systemic chemotherapy. In some instances, because of difficulties in obtaining complete histological material from referring institutions, adequate histological review was not possible.

A diagnosis of spinal cord or cauda equina compression was accepted on the basis of either clearly documented and clinically consistent symptoms and signs or myelographic evidence of disease.

Treatment of cord compression involved the use

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of radiotherapy, laminectomy, dexamethasone or a combination of modalities. In most cases, radiotherapy comprised treatment of involved fields using a dose of 20 to 30 Gy in 5 to 10 fractions. All patients initially received parenteral dexamethasone 4 mg every 6 h. After 1 to 3 days they received this drug by mouth, with subsequent tapering of dosage. Treatment consisted of radiotherapy alone in 21 instances and 6 patients received radiotherapy after decompression laminectomy. Four patients received no additional therapy, including 1 with a root lesion, 1 with a normal myelogram and 2 whose general condition and complete paraplegia made active treatment inappropriate.

Function following definitive therapy was divided into 4 groups: I—ambulant; II—ambulant with aids; III—wheelchair-bound; IV—bed-ridden.

Life-table estimates of survival were calculated using the method of Kaplan and Meier (1958). Survival was measured from the diagnosis of spinal cord or cauda equina compression to either the date of death or last contact with the patient.

Results

Of the 478 patients, 29 (6%) developed compression of the spinal cord or cauda equina; 2 also suffered a second episode. There were thus 31 episodes of spinal cord or cauda equina compression in this series. The median age was 68 years (range 51–83). Five patients (17%) developed spinal cord compression as the first manifestation of their prostate cancer; 27 patients had a histological diagnosis of adenocarcinoma, 1 had an anaplastic carcinoma of the prostate and in 1 the histological subtype was not recorded. One patient had a well differentiated tumour, 11 (38%) had moderately differentiated tumours, 6 (21%) had poorly differentiated tumours and in 11 (38%) the level of differentiation was not documented. At the time of initial diagnosis of prostate cancer, 8 patients (28%) had documented, active cancer in the prostatic bed, while 21 (72%) had established metastatic disease. All patients, other than those presenting for the first time, had previously received treatment for prostate cancer; 6 had undergone bilateral orchiectomy alone and 18 had received various combinations of radiotherapy, hormonal manipulation and chemotherapy.

The median duration of antecedent symptoms was 2 weeks (range 1 day–1 year). Five patients (17%) developed significant symptoms in less than 24 h. In all cases back pain was present. Other symptoms included weakness in 30 episodes (97%), sensory changes in 18 (58%) and ataxia in 2 (6.5%). In 18 episodes (58%) there was sphincter disturbance with new or worsening symptoms of difficulty in voiding or altered bowel habit.

Clinical examination revealed weakness in 30 episodes (97%), reflex changes in 27 (87%), sensory changes in 24 (77%), local bone tenderness in 23 (74%), cauda equina involvement in 5 (16%) and ataxia in 1. All patients had other evidence of bone metastases. In the 5 patients in whom the first manifestation of prostate cancer was spinal cord compression, 4 had a clinically malignant prostate on rectal examination. The finding in the fifth patient was not recorded.

Serum prostatic acid phosphatase, alkaline phosphatase and prostate specific antigen were reviewed. Elevated levels were found in all 19 patients whose serum prostatic acid phosphatase was recorded. Of 25 patients with recorded alkaline phosphatase levels, 15 (60%) were elevated. In only 6 patients was serum prostate specific antigen recorded and levels were raised in all them. There did not appear to be a relationship between absolute levels of circulating markers and treatment function after treatment.

Twenty-five events were diagnosed clinically as spinal cord compression and 6 were thought to be a cauda equina compression. A myelogram was performed in 27 cases. Of these, there were 17 confirmed spinal cord compressions and 4 cauda equina lesions; 3 patients had both spinal cord and cauda equina compression, 1 had a nerve root lesion, 1 had extradural disease without apparent compression and 1 had a normal myelogram.

There was good correlation between clinical and radiological diagnosis, with 15 of the 17 myelographically confirmed spinal cord compressions being diagnosed clinically. All cauda equina lesions were predicted clinically. Only 1 patient showed rapid deterioration in his neurological condition following myelography.

Sixteen episodes (52%) occurred in the thoracic vertebrae, 7 (23%) in the lumbosacral region, 6 (19%) in both the thoracic and lumbosacral regions and in 2 cases (6%) the site was not documented.

After completion of treatment, in 6 of the episodes the patients were ambulant, 7 required walking aids, 5 were wheelchair-bound and 13 were bed-ridden. No patient who was paraplegic prior to therapy regained useful function. A urinary catheter was left *in situ* in 17 patients.

The level of function achieved was not affected by the duration of symptoms. There was a significant relationship between the ability to walk before treatment and the level of function after treatment ($P=0{\cdot}015$), although pre-treatment performance status (Miller *et al.*, 1981) was not a prognostic indicator with regard to function. The 5 patients who presented with symptoms of less than 24 hours' duration remained either confined to a wheelchair or bed-ridden despite treatment.

The median time from the initial diagnosis of prostate cancer to cord compression was 118 weeks (range 0–604). The overall median time from cord compression diagnosis to death was 18 weeks (95% CI 8–22). The median survival from cord compression for the post-treatment groups (I–IV) was 21 weeks (95% CI 7–25), 24 weeks (95% CI 19–41), 21 weeks (95% CI 16–22) and 6 weeks (95% CI 5–8) respectively ($P=0.004$). One patient remains alive and is able to walk with assistance 110 weeks after the diagnosis of cord compression.

The median survival of the 5 patients in whom cord compression was the first indication of prostate cancer was 25 weeks (range 1–110+). Two of these patients were able to walk following treatment and the others were either confined to a wheelchair or bed-ridden.

Discussion

Compression of the spinal cord or cauda equina is a well recognised complication of prostate cancer, with a reported incidence of between 1 and 12% (Veith and Odom, 1965; Constans *et al.*, 1983; Kuban *et al.*, 1986; Liskow *et al.*, 1986). The importance of early detection and appropriate management of this syndrome is also generally accepted (Wright, 1963; White *et al.*, 1971; Iacovou *et al.*, 1985), although there is a lack of awareness of its importance in the management of advanced prostate cancer.

This study has confirmed that spinal cord and cauda equina compression occurs in a similar proportion (6%) to that of previously reported patients with prostate cancer. In addition, it has been demonstrated that active management is warranted in patients with some lower limb function at presentation, since 13 of the 29 patients were able to walk either with or without assistance following therapy.

The 5 patients who were not previously diagnosed as having prostate cancer represent an important sub-group of patients who present with spinal cord compression without a prior diagnosis because of the relative success of treatment. The incidence of spinal cord compression as the first manifestation of a malignancy has been estimated at approximately 10% (Veith and Odom, 1965; Gilbert *et al.*, 1978; Constans *et al.*, 1983). Histological diagnosis may require a number of investigations, including laminectomy and biopsy. In 4 patients who presented *de novo*, rectal examination revealed a frankly malignant prostate. Thus rectal examination should remain a critical component in the assessment of a patient with spinal cord compression without a primary diagnosis.

Delay in the diagnosis of spinal cord compression may result in significant neurological deterioration (Maurice-Williams and Richardson, 1988). The duration of symptoms was difficult to assess, as some patients had long-standing pain at the site of future cord compression. It is recognised that symptoms, particularly pain, may be present for many months (Veith and Odom, 1965; Constans *et al.*, 1983). Five patients presented within 24 h of the onset of symptoms and all have significant deficits despite therapy. Sixteen patients (52%) had symptoms for 2 weeks or less. In these patients, the functional outcome was related to pre-treatment function. Two patients appeared to have a delay of 1 week in the diagnosis of spinal cord compression prior to referral to this unit. Both were bed-ridden following treatment.

There was a high correlation between the clinical and radiological diagnosis. Although a recognised complication of myelography in this context is an acute deterioration in the neurological state (Torma, 1957; Sebugwawo and Hoddinott, 1987), only 1 patient in the present series appeared to suffer this complication. This may be due to the use of steroids and subsequent active management of the spinal cord compression.

Our findings regarding a predilection for thoracic vertebrae and an increased incidence among higher grade tumours support the findings of other studies (Constans *et al.*, 1983; Kuban *et al.*, 1986; Liskow *et al.*, 1986). However, this study did not confirm the relationship between grade and functional outcome as described by Kuban *et al.* (1986) and there was no correlation between the levels of serum alkaline phosphatase, prostatic acid phosphatase and prostate specific antigen as markers of disease activity and functional outcome. The present series did, however, confirm that pre-treatment function was a significant predictor of post-treatment function.

Survival following spinal cord compression was substantially shorter in patients who responded poorly to treatment and who were left with residual neurological deficits severe enough to confine them to bed. These patients had a median survival of only 6 weeks, while those who walked out of hospital had a median survival of 21 weeks. This retrospective study was not designed to compare outcomes from radiotherapy and laminectomy, and any such assessment of our data would be subject to significant bias. The question of which of these constitutes the optimal therapy has been addressed by other studies (Iacovou *et al.*, 1985; Latini *et al.*, 1989).

The duration of antecedent symptoms did not predict the functional outcome following treatment. This was not surprising, for many patients developed only mild to moderate features over weeks while others appeared to develop complete paraplegia in a matter of hours.

In summary, spinal cord and cauda equina compression is a relatively common complication in patients with prostate cancer and the symptoms and signs associated with this syndrome are well defined. The functional outcome is predicted by pre-treatment function and early diagnosis and therapy are therefore essential.

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PAEDIATRIC UROLOGY

Vesicoureteric Reflux in Sibships

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Summary—A family with 4 of 6 siblings manifesting vesicoureteric reflux is presented. Reflux could not be demonstrated in preceding and succeeding generations in this family.

Genetic analysis suggests that most instances of familial vesicoureteric reflux arise secondary to expression of autosomal dominant single genes with incomplete penetrance.

Screening of sibships for reflux might be most appropriately carried out by urine analysis, culture and ultrasound imaging.

Vesicoureteric reflux leads to morbidity in children from urinary tract infections, pyelonephritis and occasional renal failure (Zimmerman *et al.*, 1973). Reflux is reported to be present in less than 1% of children in the general population and 8 to 45% in siblings of children with reflux (Bredin *et al.*, 1975; Schmidt *et al.*, 1972). We present a family in which 4 of 6 siblings exhibited reflux. Because of uncertainty about the injury incurred by the kidneys secondary to reflux, screening for reflux in families must be selective, cost-effective and minimally invasive. Based on this family and on what is known about genetic predisposition, a plan is proposed for reflux screening within sibships.

Patients and Methods

The study family consisted of 3 generations (Fig. 1). Four male and 2 female children comprised the index generation. The index child presented at the age of 8 years with a history of urinary tract infections and underwent intravenous urography (IVU) and voiding cystourethrography (VCUG). Subsequently, the 5 remaining members of the index generation were similarly evaluated. The preceding generation was evaluated when the mother became a potential kidney donor. Investigations included urine analysis, IVU, VCUG and histocompatibility testing. The father refused evaluation despite having a sister who was thought to have had "renal disease". The generation succeeding the index generation consisted of 9 children (5 males and 4 females) and 3 members of this generation (2 females and 1 male) were evaluated by urine analysis and ultrasound. The one female child with a history of a urinary tract infection also underwent VCUG.

Results

Four (2 males, 2 females) of 6 siblings in the index generation had reflux (Fig. 1). The index patient had grade 4/5 right-sided reflux on VCUG and bilateral caliectasis on IVU. He underwent right ureteroneocystostomy without further reflux or urinary tract infections.

A 3-year-old male sibling with a history of urinary tract infections showed a scarred right kidney on IVU (Fig. 2), grade 3/5 left-sided reflux on VCUG (Fig. 3) and abnormal ureteric orifices bilaterally. Bilateral ureteroneocystostomy was performed without complications. He developed renal failure 8 years after ureteroneocystostomy and underwent living related renal transplantation from his mother. The aetiology of his renal failure was not identified since neither native nephrectomies nor renal biopsy were performed. Obstruction, urinary tract infection and recurrent reflux were not present on ultrasound, urine culture and repeat VCUG.

Two female siblings demonstrated reflux, 1

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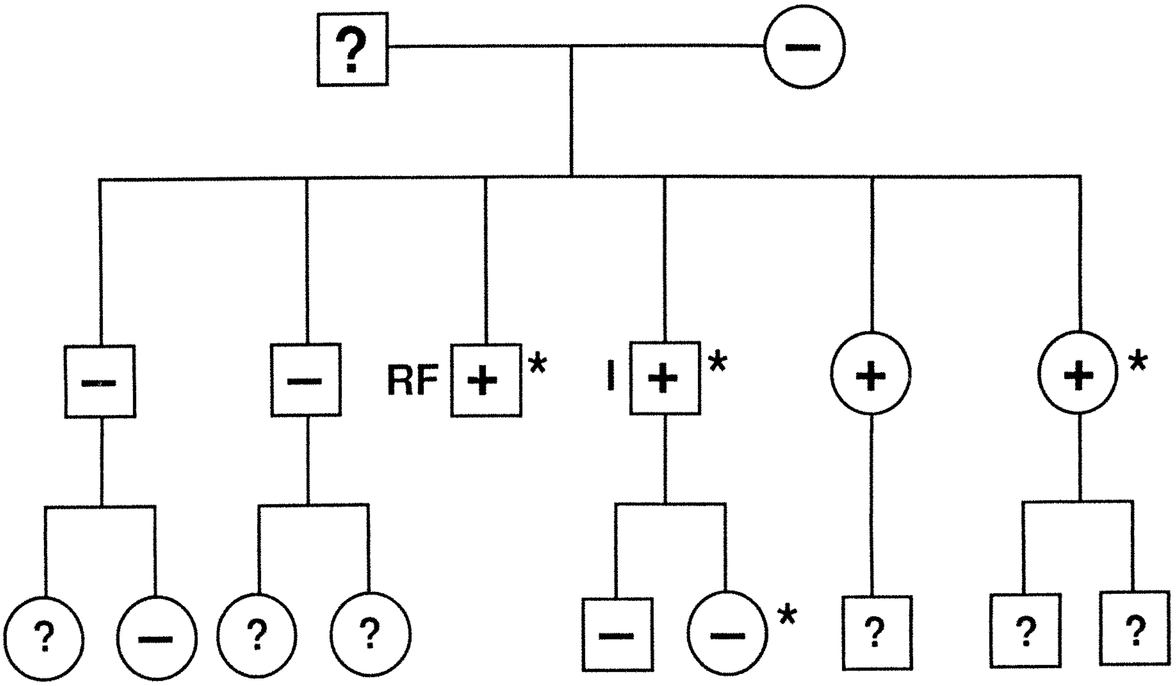

Fig. 1 Results of evaluation. □ = male. ○ = female. I = index case. ? and ? = not evaluated. * = history of urinary tract infection. + = vesicoureteric reflux. − = no vesicoureteric reflux. RF = renal failure.

having a history of urinary tract infection. VCUG revealed grade 2/5 left-sided reflux in the female sibling with a history of urinary tract infection. The asymptomatic female sibling had grade 1/5 bilateral reflux. The reflux of both female siblings stopped without surgery. Two other male siblings did not have reflux.

Two individuals in the generation preceding the index generation were available for evaluation. The mother did not reflux on VCUG at the time of her kidney donation. The asymptomatic father refused evaluation.

Three of 9 members of the generation succeeding the index case were evaluated by urine analysis, ultrasound, or VCUG. Reflux was not found, although 1 of the 3 evaluated children has a history of a urinary tract infection. The parents of remaining members of this generation have declined further evaluation of their children.

Discussion

The modes of inheritance in familial reflux and the extent of genetic heterogenicity are not well defined. Genetic analysis of most sibships with reflux has suggested an autosomal dominant gene defect with incomplete penetrance and variable expression (Chapman *et al.*, 1985). Sex-linked recessive and multifactorial inheritance patterns have also been postulated (Lewy and Belman, 1975; Middleton *et al.*, 1975; DeVargas *et al.*, 1978; Torres *et al.*, 1980). According to the autosomal dominant hypothesis, the chances for an individual who inherits the reflux gene to have reflux as an infant and adult are 75 and 45% respectively, and 15% of those with the gene will eventually develop renal failure. The possibility of a multifactorial mode of inheritance cannot be excluded in the family reported here. However, in such a model, it would be highly unusual for 4/6 siblings in a single generation to have reflux. Autosomal recessive inheritance remains a possibility, but such a mechanism cannot be assumed solely on the basis of recurrence within a sibship. The information available on this family is most consistent with dominant inheritance with incomplete penetrance. However, this hypothesis remains unproven because of the absence of documented reflux in preceding or subsequent generations and the refusal of some critical family members to be completely evaluated.

Vesicoureteric reflux appears to be associated with certain HLA haplotypes including HLA-B12 in females, HLA-B8 in combination with HLA-A9 or HLA-B15 in males, and HLA-B15 alone in both sexes (Sengar *et al.*, 1979; Torres *et al.*, 1980). Two of the affected members of the family reported here

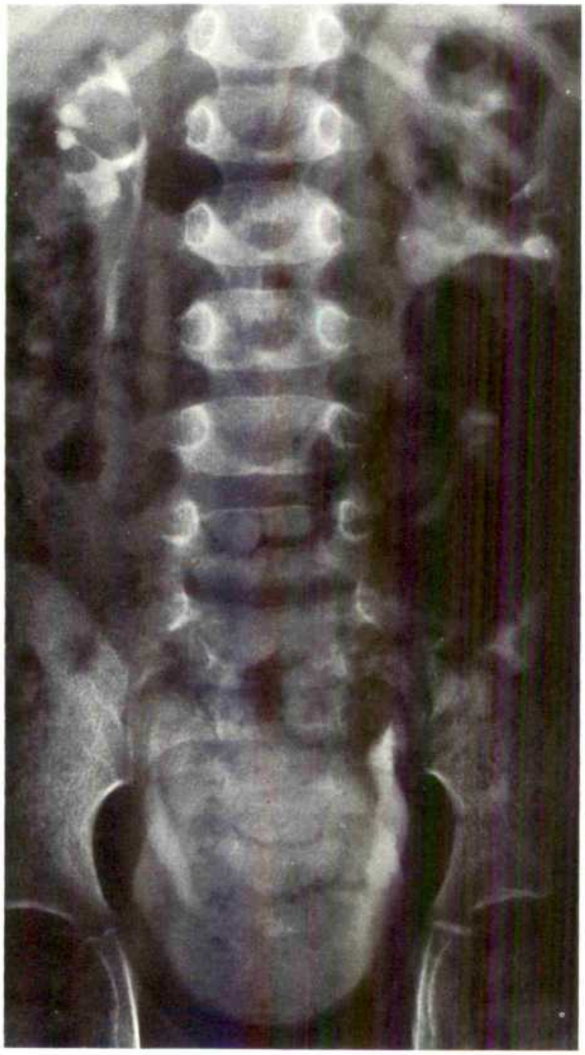

Fig. 2 IVU of 3-year-old male sibling of index patient. Note scarred right kidney with left upper pole caliceal dilatation.

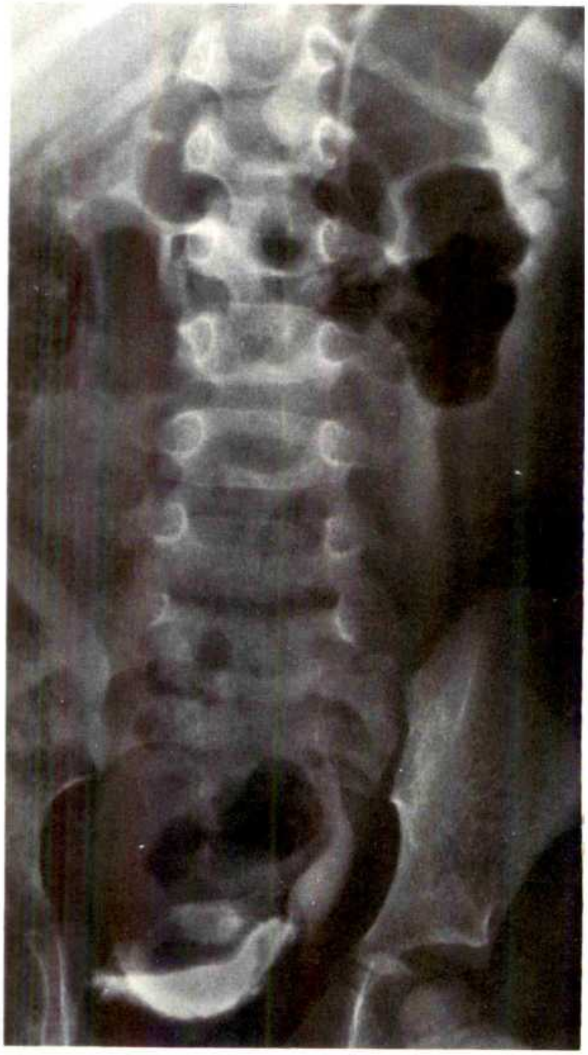

Fig. 3 VCUG (post-void film) of 3-year-old male sibling of index patient. Note grade 3/5 left-sided reflux. Similar findings were observed in the voiding film.

have undergone HLA typing and neither member has these haplotypes. While theoretically interesting, histocompatibility testing would not seem to play a major role in either screening or management of reflux.

This raises the question of who should be screened and how. Genetic priorities for screening members of families should probably be based on the dominant gene with incomplete penetrance hypothesis. Members of the sibship have the highest priority for screening on a purely genetic basis. The next highest priority for evaluation is the offspring of known refluxers, who have a 50% chance of inheriting the gene and a resultant risk of showing reflux in infancy of 35% [0.5 × 0.75]. The unstudied father in this family would have the next highest priority. He has a high likelihood of being a carrier of this gene (higher because of the normal evaluation of his spouse). If he has this gene, he would have a 45% chance of showing reflux at his age and a 15% chance of developing renal failure. The lowest priority for screening would be for the offspring of unaffected children. These children would have a 6 to 8% chance of being clinically affected (Pauli and Motulski, 1981). Screening of second degree relatives might be considered optional, since the relative risk of reflux is low unless they have had urinary tract infections.

Recommendations for reflux screening have included VCUG, IVU, radionuclide cystography and ultrasonography. Jerkins and Noe (1982) screened 104 siblings of index patients using VCUG and demonstrated reflux in 32% (73% of whom were asymptomatic). Siblings with reflux underwent IVU to assess the degree of renal scarring. When index patients had both reflux and renal scarring, 50% of their siblings showed reflux. When the index patient had reflux only, 26% of siblings had reflux. This suggests that the more severe the reflux in the index patient the greater is the rationale for screening family members. Radionuclide cystography has also been used for reflux screening among 60 asymptomatic siblings of patients with reflux; 45% showed reflux on nuclide cystography, an incidence similar to that detected by conventional X-rays (Van den Abbeele *et al.*, 1987). While the ability to concentrate urine may be the earliest physiological marker for reflux, no experience with the use of concentrating ability as a screening test for reflux has yet been reported. It might be presumed that the more severe degrees of reflux (such as those associated with IVU changes) might be associated with the more severe impairments in concentrating ability (Uehling, 1971; Uehling and Wear, 1976). However, we have encountered problems in parental compliance with withholding children's fluid intake for the necessary 14 to 16 h. Thus we would not expect concentrating ability to be a reliable out-patient screening method. A systematic comparison of methods for screening for familial reflux has not been carried out. However, comparison of ultrasound, IVU and VCUG in detecting anatomical abnormalities in children with recurrent urinary tract infection (not sibships) showed that ultrasound alone was sufficiently sensitive to identify all of those individuals who required surgery, and missed only the more minor degrees of reflux (Alon *et al.*, 1986). Holland *et al.* (1990) reported the importance of vesicoureteric reflux plus urinary tract infection, but not the severity of reflux, in the evolution of renal scarring seen on dimercaptosuccinic acid scans. Based on all of these considerations, a plan for reflux screening can be suggested.

A cost-effective, non-invasive screening plan for asymptomatic first-degree relatives might include ultrasound, urine analysis and urine culture. Any sibling with an ultrasound abnormality or infection would then have a voiding cystourethrogram. We are currently recommending this plan for reflux screening in sibships but do not have sufficient experience adequately to validate its advantages and pitfalls. Screening by urine analysis, culture and ultrasound imaging also reflects our belief that the lesser degrees of reflux are best managed nonsurgically. Those who feel differently may wish to carry out cystography on all of the members of a sibship in which 1 member manifests reflux.

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Multicystic Renal Dysplasia Detected by Prenatal Ultrasonography. Natural History and Results of Conservative Management

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Summary—In a review of 44 infants with multicystic renal dysplasia diagnosed prenatally by ultrasonography, contralateral anomalies, bilateral disease and other non-urinary congenital anomalies were rare. In approximately two-thirds of infants the lesion was impalpable and in 2 cases involution had ocurred prenatally. All but 5 were managed conservatively and without complications, and partial or complete involution of the lesion occurred in more than 50% during follow-up. It was concluded that the natural history of this anomaly is usually benign and that conservative management is advisable.

In recent years the diagnosis of congenital multicystic renal dysplasia has been transformed by the introduction of ultrasonography and static isotope scintigraphy (Hartman *et al.*, 1986). At the same time, the number of cases detected has increased substantially as a consequence of prenatal ultrasonography. Conventional management has been nephrectomy; should this also be transformed?

Patients and Methods

We have reviewed 44 patients with multicystic renal dysplasia, detected by prenatal ultrasonography, who presented to this unit between 1979 and 1989. When postnatal ultrasonography was consistent with this diagnosis, static scintigraphy with ^{99m}Tc dimercaptosuccinic acid (DMSA) was performed when the child was about 1 month old. An intravenous urogram was performed if there was doubt as to the normality of the contralateral upper renal tract. Conservatively managed patients were followed up by means of ultrasonography at 6-monthly intervals until they were 2 years of age, and then annually to 5 years of age. Growth and blood pressure were checked at each visit. Thereafter the patients were returned to the care of their general practitioner with a recommendation that blood pressure be recorded annually.

Results

Of the 44 patients, 32 (73%) were boys. The lesion was left-sided in 21 cases and bilateral in 1. When it was known, the gestational age at which the condition was detected was <20 weeks (2 cases), 20–30 weeks (4) and >30 weeks (10). In 17 cases the prenatal diagnosis had been hydronephrosis rather than cystic dysplasia. Two fetuses had the typical appearances of multicystic dysplasia at 28 to 30 weeks' gestation, yet substantial involution of the lesion had already occurred by birth.

The lesion was palpable during the neonatal period in 16 patients (36%). One of these had bilateral disease and in another the kidney lay in the false pelvis rather than orthotopically. Two patients had contralateral urinary anomalies: 1 a minor degree of pelvicaliceal dilatation which resolved spontaneously by 6 months of age and the other a non-refluxing, non-obstructed megaureter which had partially resolved by 3 years of age. Non-urinary anomalies were 1 aortic coarctation and 1 dislocated hip.

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All ^{99m}Tc DMSA scintigrams showed no uptake of isotope by the affected kidney and compensatory hypertrophy of the opposite kidney. During the period reviewed there were 3 other cases of multicystic dysplasia not detected by prenatal ultrasonography, all presenting before 1983.

Progress

The infant with bilateral disease rapidly succumbed to pulmonary insufficiency. Five patients early in the series underwent nephrectomy. In one, where surgery was deferred until 3 months of age, the lesion, which was readily palpable at birth, had become involuted and proved difficult to locate.

Conservative management was employed in 38 patients, of whom 5 have been lost to follow-up. In the remaining 33, follow-up ranged from 14 to 72 months (mean 36), during which time the patients' growth and development have been normal and there has been no instance of hypertension. Current ultrasound examinations show no change in 14 instances, partial involution of the lesion in 9 (Fig.) and complete involution, with no residuum detectable, in 10. The last finding was most common in patients with the longest follow-up.

Discussion

In this area, multicystic renal dysplasia is always diagnosed by prenatal ultrasonography rather than by clinical means. Our patients resemble those in previous reports, where the diagnosis was made clinically, in terms of lateralisation and sex distribution but not in the proportion with contralateral urinary anomalies or bilateral disease (7%). In earlier series, these were recorded in 32% (Johnston, 1971) and 50% (Pathiak and Williams, 1964).

Although it has long been suspected that multicystic kidneys do not grow with the patient, serial ultrasonography now reveals that the natural history of these lesions is generally one of spontaneous involution, a process which may, on occasion, commence prenatally (Avni *et al.*, 1987). Evidently a "solitary kidney" in an older patient may in reality represent the involution of multicystic dysplasia.

In the present series, almost two-thirds of lesions were impalpable even though the examiner was aware of the sonographic findings. From a population of approximately 3,000,000, we currently see an average of 8.5 new cases of multicystic kidney *per annum*. If two-thirds of these had remained undetected but for prenatal ultrasonography, this would extrapolate to approximately 105 cases each year in the United Kingdom as a whole (population 56,000,000).

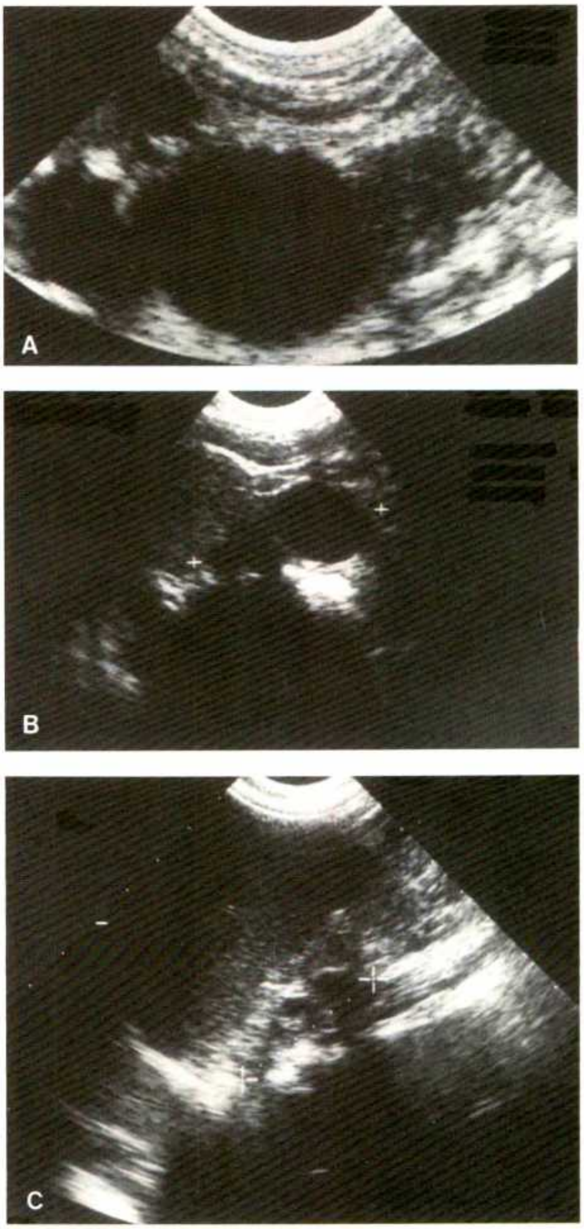

Fig. Ultrasonography showing spontaneous involution of cystic dysplastic kidney. (A) Aged 1 month. (B) Aged 9 months. (C) Aged 21 months.

Is it safe to leave these lesions *in situ*? Occasional reports have described infection (Hartmann *et al.*, 1986) or spontaneous perforation (Knutrud, unpublished data) of cysts. More significant are examples of hypertension (Ambrose *et al.*, 1982) and of malignant change (Birken *et al.*, 1985). Taken together, these amount to no more than 15 reported cases over 20 years (Gordon *et al.*, 1988) and so the risk seems slight, bearing in mind the substantial number of cases which previously passed undetected. Conservative management thus appears a satisfactory option, a material consideration at a time of economic constraint and when the number of diagnosed cases is increasing.

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British Journal of Urology (1992), **69**, 541–548

Case Reports

Localised Infarction of the Testis

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Case Report

A 52-year-old man was admittted with a 24-h history of left testicular discomfort which had developed while he had been changing for bed. He had no other symptoms and no relevant past medical history.

Examination was normal apart from a slightly tender left testis.

A full blood count, erythrocyte sedimentation rate, urine microscopy and culture, beta-HCG and alpha-fetoprotein were normal but a scrotal ultrasound examination revealed a 16-mm hypoechogenic lesion within the upper pole of the left testis suggestive of a malignant tumour.

A radical orchiectomy was performed from which the patient made an uneventful recovery.

Histology failed to demonstrate any malignancy but showed a pale area of localised infarction with thrombosis of a small neighbouring vessel.

Comment

Complete infarction of the testis may occur following torsion or trauma. Localised infarction seldom occurs, with only 9 reported cases and in association with a number of conditions, *e.g.* polycythaemia, sickle cell disease, hypersensitivity angiitis and trauma (Jordan, 1987; Baer *et al.*, 1989). In this case it occurred in the absence of any other detectable pathology but, as with the other cases, led to orchiectomy on the suspicion of malignancy.

Scrotal ultrasound is an accurate investigation for distinguishing testicular from non-testicular swellings, but it is less satisfactory in distinguishing benign from malignant swellings within the testis, and a false positive rate of 50% has been reported (Tackett *et al.*, 1986). With its increasing use it is likely that ultrasound scanning will detect benign conditions such as localised infarction more frequently and unless these can be differentiated from malignant lesions this will lead to a number of unnecessary orchiectomies.

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Perforation of Bladder Carcinoma Presenting as Acute Abdomen

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Case Report

A 77-year-old woman presented with a 2-day history of suprapubic pain radiating to the left iliac fossa. Her relatives reported that she had complained of urinary incontinence over the preceding month.

On examination she was pyrexial (39.1°C), confused and dehydrated. Examination of the abdomen revealed generalised tenderness and rigidity, most marked in the left iliac fossa.

Investigations showed a leucocytosis but plain films of the abdomen were normal. Urethal catheterisation produced a small amount of urine which had a high white cell count on microscopy. The patient was resuscitated with intravenous fluids and antibiotics.

At laparotomy, the peritoneal cavity contained approximately 600 ml of cloudy fluid and a marked fibrinous exudate. The dome of the bladder was replaced by a large tumour with a perforation 1.5 cm in diameter on the left side (Fig.). The bowel and uterus were not involved but the bladder tumour was fixed to the side walls of the pelvis.

Peritoneal toilet was performed and a suprapubic catheter was placed in the bladder. Biopsies were taken and the perforation was closed and covered with an omental patch. No definitive surgical procedure was possible because of the fixity of the tumour and the patient's poor clinical condition.

The patient made a good post-operative recovery. Histology showed a poorly differentiated squamous cell carcinoma of the bladder. Intravenous urography showed hydronephrosis and hydroureter bilaterally.

Comment

Spontaneous intraperitoneal rupture of the bladder through a carcinoma is a rare event. Only 2 cases

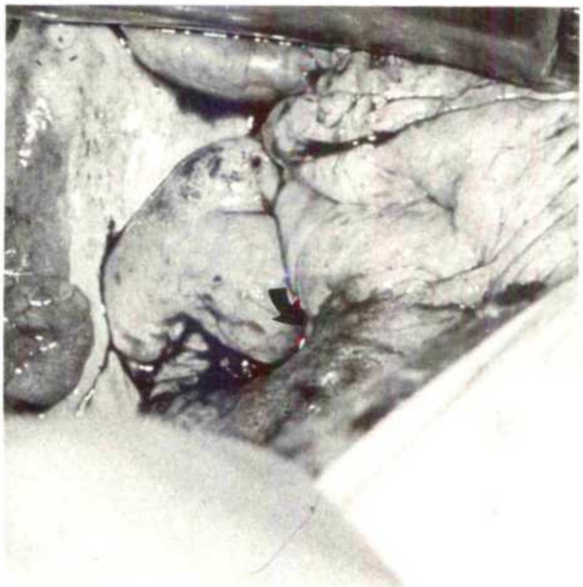

Fig. Intra-operative view of urinary bladder with arrow at site of perforation.

have previously been described in females (Glashan, 1957; Jenkinson, 1981). The classical history is of a sudden onset of lower abdominal pain, often occurring during micturition, followed by inability to pass urine (Thompson *et al.*, 1961). This may be preceded by dysuria followed by oliguria or anuria. The investigation of choice is cystography, but the symptoms and signs are generally not specific enough for a pre-operative diagnosis to be made. The mortality rate in undiagnosed cases may be as high as 80%. The prognosis of spontaneous rupture of a carcinoma is poor.

The treatment of choice is cystectomy, but the clinical condition of the patient may limit operative treatment to excision of the segment of perforated bladder, bladder drainage and closure followed by intensive peritoneal lavage. The diagnosis should be considered in all cases of acute abdomen, especially in patients with pre-existing or recent onset of urinary symptoms.

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Generalised Seizure after Extracorporeal Shock Wave Lithotripsy. A Complication Easy to Prevent?

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Urologists are inclined to instruct their patients after stone treatment to drink as much as possible.

Case Report

A 41-year-old woman with normal renal function (creatine 60 µmol/l), suffering from chronic urinary tract infections with *Proteus mirabilis*, caused by a 14 × 7 mm stone in the lower pole of the renal calix, but otherwise healthy, was treated with the HM-3 Dornier lithotriptor (ESWL). Successful disintegration was achieved with 700 19 kV shocks. Recovery was uneventful until the first day following treatment, when the patient lost consciousness and developed a generalized seizure with urinary incontinence; 10 mg diazepam were given intravenously.

Neurological examination revealed no focal abnormalities apart from low serum concentrations of sodium (119 mmol/l), chloride (87 mmol/l) and urea (1.5 mmol/l). Normal values in this laboratory are sodium 136–148 mmol/l, chloride 97–109 mmol/l and urea 2.5–8.0 mmol/l. She was treated with 1.5 L sodium chloride 0.9% intravenously over 12 h, followed by 2 g NaCl orally 3 times daily for 24 h. Over a period of several hours she regained full consciousness (E4, M5, V5). Follow-up for 6 years has revealed no abnormalities.

Comment

As her fellow-patients had noticed, this patient followed too enthusiastically the advice to drink liberally; she drank more than 5 L tap water in 12 h, resulting in hyponatraemia due to dilution.

This appears to be the first reported case of hyponatraemia in relation to ESWL treatment.

Rapidly developing hyponatraemia is a well known phenomenon in urology (endoresection of the prostate), in internal medicine (rapid rehydration after dehydration due to severe diarrhoea), in psychiatry (compulsive behaviour) and in alcoholism (excessive consumption of water due to gastritis). The severity of neurological disorders is related to the rapidity of the decrease in sodium concentration, but the sodium concentration itself also influences the clinical picture (Ayus *et al*., 1985; Arieff *et al*., 1976). When hyponatraemia develops rapidly, correction should also be rapid (2 mmol/l/h) to prevent death (Ayus *et al*., 1985). However, correction exceeding 2 mmol/l/h may cause central pontine myelinolysis (Sterns *et al*., 1986).

Urologists must be careful in their instructions to their patients and a general encouragement to "drink plenty of water" can be dangerous if the volumes are not specified.

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Fournier's Gangrene: an Aetiological Hypothesis

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In 1884, Fourier described a condition of fulminating gangrene of the genitalia. Since then, less than 400 cases have been described. We present 2 cases and speculate on a possible aetiological mechanism of this rare condition.

Case Reports

Case 1. T.N., a 63-year-old gentleman, presented with a 9-day history of anal pain. At operation a large ischiorectal abscess was found and drained. Six hours later a pyrexia of 39.7°C was noted. The following day swelling of the genitalia was observed. The pyrexia persisted despite antibiotics. Blood cultures at this time were negative. The following day, ischaemic areas were noted over the scrotum and these were treated by radical debridement. Cultures from the infected tissues grew *Streptococcus mitis* and mixed coliforms. It was necessary to perform a further debridement the following day. Once the gangrene was controlled, healing was rapid. An attempt at skin grafting the scrotum failed, but an excellent cosmetic and functional result was obtained from conservative treatment.

Case 2. D.A., a 43-year-old gentleman, was admitted with a 1-week history of a perianal abscess. At presentation, gangrene and necrosis of the perineal skin were noted (Fig.). He was immediately taken to theatre for debridement of the perineal, scrotal and inguinal skin. Infection was also spreading into the para-rectal space and a laparotomy and Hartmann's type procedure were performed. Cultures from the pus showed a mixed flora, including anaerobic streptococci. Post-operatively, the patient developed a disseminated intravascular coagulopathy and was also found to be an insulin-dependent diabetic. During this time the infection spread to involve the whole para-rectal space, including the rectal stump itself, requiring excision of the rectum with sparing of the perineal floor.

The patient made slow but steady progress and was transferred to a plastic surgery unit for reconstruction of the scrotum and perineum.

Comment

The aetiology of Fournier's gangrene is poorly understood. However, it is clear from reviewing the pooled data of 86 cases, from a total of 400 cases in

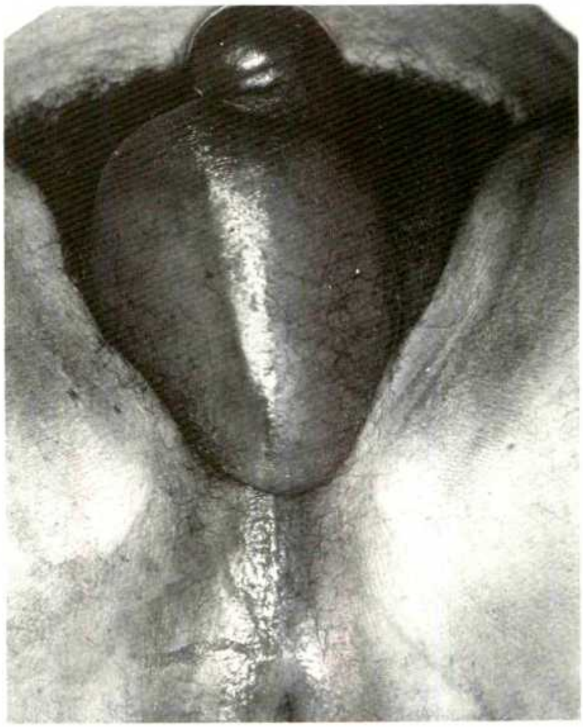

Fig. Gangrene of scrotum and surrounding tissues.

the literature, that certain themes are common to most cases.

Fournier described 3 characteristics of the disease.

(1) Abrupt onset in healthy young adults
The average age of the 86 patients was 50.1 years (range 25–74) and chronic disease was present in over 50%. Diabetes was present in 15/62 patients (24%). A review of 20 case reports suggested that prodromal symptoms, usually scrotal pain, were extremely common. These were present for a mean of 3.5 days (range 1–7).

(2) Rapid progression
This was a common feature once gangrene had become established (Bahlmann *et al.*, 1983; McGeehan *et al.*, 1984; Riegels-Nielsen *et al.*, 1984).

(3) Unknown aetiology
Peri-urethral sepsis secondary to an established stricture or instrumentation was found in 46/79 patients (58%), and peri-anal or peri-rectal sepsis in 32/79 patients (41%). Thus sepsis was found in 99% of cases. Microbiologically, where anaerobes were sought, both *Bacteroides* and *Clostridia* were common *Escherichia coli*, *Proteus* and *Klebsiella* were common amongst the gram-negative aerobes.

The existence of a prodromal phase and a pattern of spread which usually spares the testes and the skin of the anal margin, both of which have an alternative blood supply, suggest that this condition may originate in ischaemic tissues. The high incidence of diabetes and debilitating illness supports this hypothesis. In addition, the Hartmann's type procedure in case 2 may well have compromised the descending blood supply to the rectum, rendering it vulnerable to the advancing necrosis.

As both peri-urethral and peri-anal sepsis produce the same pattern of disease, it is possible that the infection originates in an area common to both of these systems, *i.e.* the superficial perineal space. The superficial branches of the internal pudendal artery supplying the scrotum run through this space. Infection and interruption of the blood supply to the scrotum would provide the ischaemic conditions necessary to initiate the process and the diminished host response, which occurs in chronic disease, would assist propagation of the infection and development of gangrene.

In summary, we postulate that infection originating in the urinary tract or the distal gastrointestinal tract may spread to the superficial perineal space. This may in turn affect the local blood supply, rendering the tissues ischaemic. In individuals who are susceptible through chronic illness a synergistic type gangrene may supervene, producing the full blown condition. Radical debridement in association with broad spectrum antibiotics remains the treatment of choice, but the mortality rate in the 84 cases reviewed was 24%.

Acknowledgement

We thank Professor M. Baum for allowing us access to this patient for the preparation of this report.

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Paneth and Argyrophil Cells in Prostatic Carcinoma

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Case Report

A 68-year-old man who presented with dysuria had an enlarged, hard, nodular prostate and an elevated serum acid phosphatase. Ultrasound and computed tomography demonstrated that the prostatic capsule was infiltrated. Following transurethral resection, the patient was treated with anti-androgens and to date (18 months later) he is well. Histology revealed a widespread infiltrating carcinoma (grade II Gaeta). Typical Paneth cells were identified in many neoplastic tubules, appearing, as in our control on duodenal mucosa, bright red with Lendrum's phloxine-tartrazine, pink with Lillie's azure A-eosin, bluish black with phosphotungstic acid haematoxylin (Fig. 1) and PAS-positive, but Grimelius, Alcian

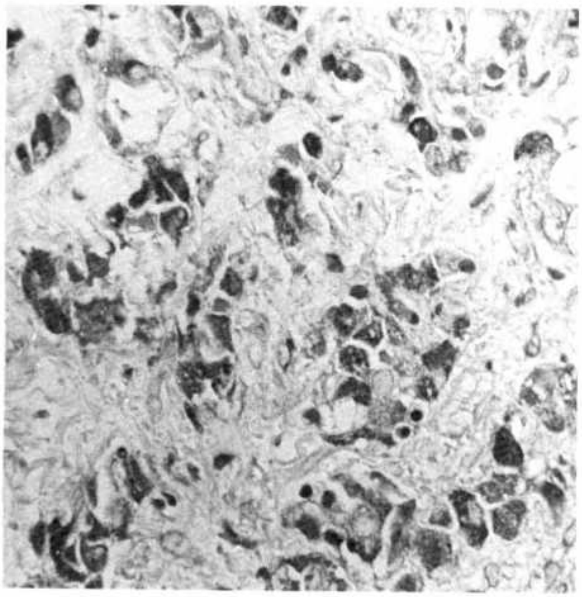

Fig. 1 Prostatic carcinoma. Paneth cell granules are strongly stained with Lillie's azure A-eosin B method (× 125).

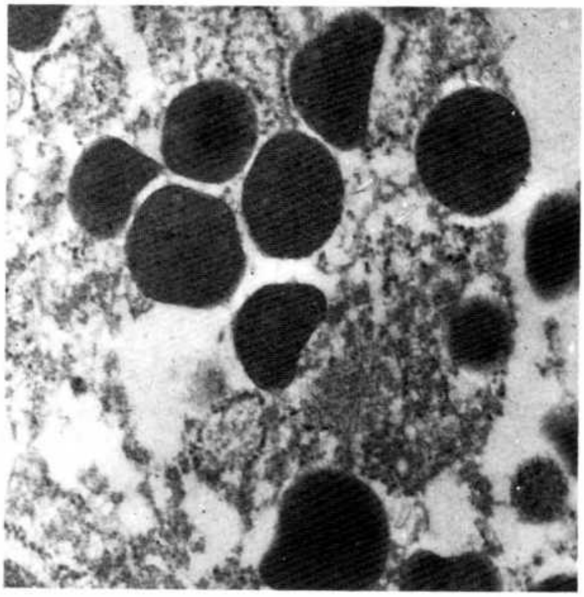

Fig. 2 Round dense homogeneous granules in the apical cytoplasm of Paneth cells in prostatic carcinoma (original magnification × 20,000).

blue and Masson-Fontana argentaffin negative. Argyrophil cells, Grimelius-positive, were scattered irregularly among neoplastic tubules. The ABC-immunoperoxidase technique showed prostatic acid phosphatase and prostatic specific antigen in almost all carcinoma cells, including the argyrophil, but not in the Paneth cells, which were intensely stained with antilysozyme. In the Paneth cells, electron microscopy demonstrated spherical granules of various density and a diameter between 400 and 900 nm, slightly smaller than the control (Fig. 2). Smaller granules of 100–200 nm were found in the argyrophil cells.

Comment

The presence of argyrophil and argentaffin cells has been well described in normal and hyperplastic prostates (Capella *et al.*, 1981) and are also found in 8 to 30% of prostatic carcinomas (Stratton *et al.*, 1986). The presence of Paneth and argyrophil cells in prostatic carcinoma, previously reported only by Haratake *et al.* (1987), supports the existence of mixed and/or metaplastic carcinoma. We believe that these cells derive from local precursor or common stem cells.

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Giant Bladder Diverticulum Causing Urethral Obstruction in an Infant

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Giant bladder diverticula in male infants rarely cause retention of urine. A 13-month-old male is reported whose sudden urinary retention was caused by a low-lying diverticulum of the bladder.

Case Report

A previously healthy 13-month-old Caucasian male infant presented with colicky abdominal pain and lower abdominal swelling. Because of a concern for intussusception, barium enema examination was performed, the positive findings from which included elevation and displacement of the left colon from a markedly distended bladder. Subsequent micturating cystourethrography (MCU) (Fig.) and renal ultrasonography (RUS) revealed no evidence of posterior urethral valves, a large capacity bladder with smooth wall, a large diverticulum arising from the left side of the bladder, and moderate bilateral hydronephrosis. Cystoscopically the ureteric orifices were confirmed as being normal in location and configuration, with the origin of the diverticulum arising midway between the left ureteric orifice and bladder neck. The diverticulum was excised intra- and extra-vesically without reimplanting the ureter. Post-operatively the infant voids normally, and MCU and RUS show no bladder outlet obstruction or hydronephrosis.

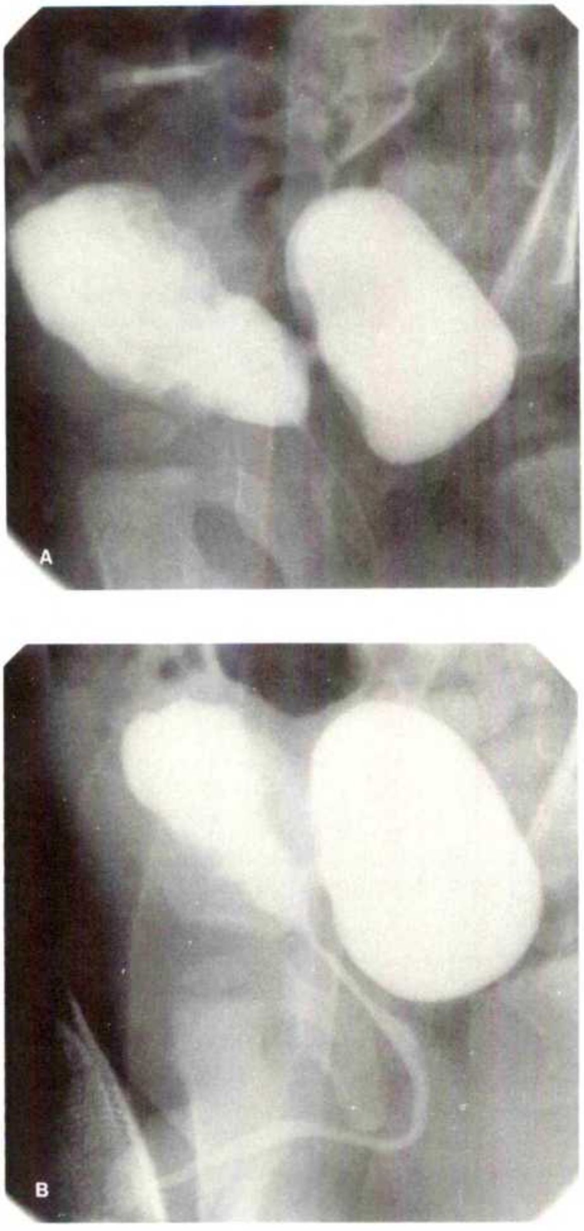

Fig. (A) MCU during filling showing large left bladder diverticulum. (B) Micturating film showing compression and elongation of urethra.

Comment

Urinary retention is uncommon in male infants and is usually caused by posterior urethral valves. Less commonly, a low placed diverticulum may be the cause rather than the result of retention of urine. It is felt that the sac enlarges downwards into the pelvis as it fills. During bladder contraction it stretches the urethra and compresses it, so that ultimately urine flows more easily into the diverticulum than down the urethra (Williams, 1974). Treatment is surgical removal of the diverticulum, as normal voiding without compression of the urethra is restored. Cases similar to ours have been reported. Taylor *et al.* (1979) reported 2 cases and found 5 similar ones in the literature. In 1984 Verghese and Belman presented 2 patients whose urethral obstruction was relieved by diverticulectomy, and they gave 3 new references involving similar cases. Valdez *et al.* (1987) and Orikasa *et al.* (1990) each reported a case and added a single new reference. Although rare, bladder diverticula should be considered in the differential diagnosis of the causes of urinary retention in male infants.

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Requests for reprints to: T. S. Parrott, 5455 Meridian Mark Road, Suite 510, Atlanta, Georgia 30342, USA.

Perineal Ectopic Testis

H. DOĞRUYOL and E. BALKAN, *Department of Pediatric Surgery, Uludağ University, Bursa, Turkey*

Case Report

R.Ö., a 2-year-old boy, was referred with left cryptorchidism. Palpation of the left inguinal area showed no evidence of a testis but examination of possible sites of an ectopic testis revealed a firm, mobile perineal mass identical in size to the right testis (Fig.).

Surgical exploration showed a fixed left gubernaculum testis in the perineum. Orchiopexy to the left hemiscrotum was performed.

Comment

Although it is the commonest form of true testicular ectopia, excluding the superficial inguinal form, perineal testis is a rare congenital anomaly (Murphy and Butler, 1985). Since John Hunter reported the first case of the disease in 1786, only 113 cases have been reported in the English and 13 cases in the Japanese literature up to 1984 (Uchijima *et al.*, 1984). Only 6 cases have been reported in the world literature between 1980 and 1985 (Lozano-Ortega *et al*, 1983; Uchijima *et al.*, 1984; Garat *et al.*, 1985).

The diagnosis is easily made by finding a mass in the perineum with an empty scrotum. The inguinal approach allows placement of the testis in the corresponding hemiscrotum without difficulty because of the long length of the cord. Since histopathological disturbances are minimal, the prognosis is better than that of cryptorchidism (Garat *et al.*, 1985).

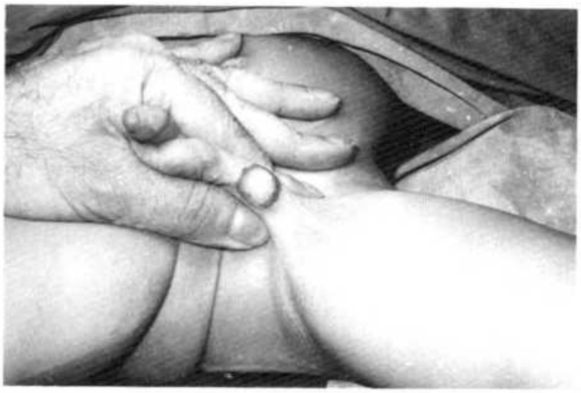

Fig. Site of the testis.

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Requests for reprints to: H. Doğruyol, Uludağ Üniversitesi, Tip Fakültesi, Çocuk cerrahisi Anabilim Dali, Duaçinar, Bursa, Turkey.

Abdominoscrotal Hydrocele

A. MEABED, A. H. KOKO, V. C. ONUORA, S. AL-MOHALHAL and A. M. YOUSSEF, *Department of Urology, Central Hospital, Riyadh, Saudi Arabia*

Case Report

A 23-year-old man was admitted with a mass in the right inguinoscrotal region; it had been increasing slowly over the previous 3 years. Examination revealed a large cystic swelling on the right side of the abdomen extending from the level of the umbilicus to the right side of the scrotum. It was non-tender, irreducible and freely mobile in the vertical direction (Fig.). A normal testis was easily palpable at the lower limit of the swelling. A vaginal hydrocele was present on the left side.

Ultrasonography and CT scan of the abdomen confirmed a cystic mass with a thin wall and homogeneous fluid. Urography revealed right ureterohydronephrosis due to pressure from the mass. An immunological test for hydatid disease was negative.

At operation it was possible to excise the cyst intact, preserving the vas deferens and the testicular vessels. Histopathological examination revealed a fibrocollagenous cyst lined by cuboidal epithelium consistent with a cyst of the tunica vaginalis.

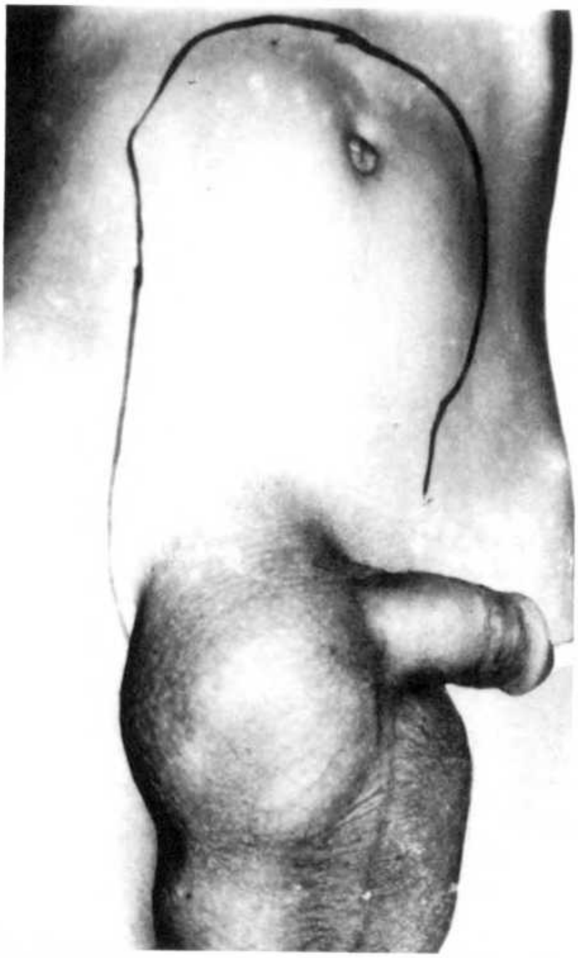

Fig. Outline of the extent of the abdominoscrotal hydrocele.

Comment

An abdominoscrotal hydrocele is thought to be a collection of fluid in the tunica vaginalis testis which extends via the internal inguinal ring into the retroperitoneum. In our patient it appeared to originate from an encysted hydrocele of the cord (Jacobsen, 1983).

The condition is benign and can cause hydronephrosis by pressure on the ureter (Lampmann *et al.*, 1984). However, a case of paratesticular malignant mesothelioma associated with an abdominoscrotal hydrocele has been reported (Velasco *et al.*, 1988).

Even with the aid of modern imaging, abdominoscrotal hydrocele can still be missed. It should be considered in the differential diagnosis of abdominoscrotal masses in both adults and children.

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Requests for reprints to: V. C. Onuora, Department of Urology, Central Hospital, P.O. Box 2897, Riyadh 11196, Saudi Arabia.

British Journal of Urology (1992), 69, 549–552
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Point of Technique

Why Renography Can Fail in the Diagnosis of Upper Urinary Tract Obstruction

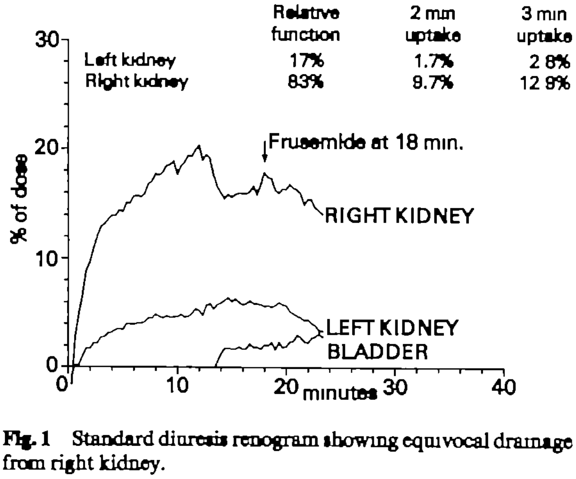
G. D. WEMYSS-HOLDEN and S. R. PAYNE, *Department of Urology, Royal Infirmary, Manchester*

Case Report

In a 26-year-old female with right loin pain the IVU appearances were those of a right pelviureteric junction obstruction. A standard diuresis renogram was terminated shortly after administration of frusemide because of right loin pain but the test suggested an equivocal drainage pattern for the right kidney (Fig. 1). A subsequent F-15 renogram (frusemide administered 15 min prior to the radiopharmaceutical) showed a rising curve for the right kidney until 28 min (Fig. 2) and then rapid excretion of tracer. The analogue images showed filling and expansion of a large right renal pelvis until 28 min and then rapid drainage.

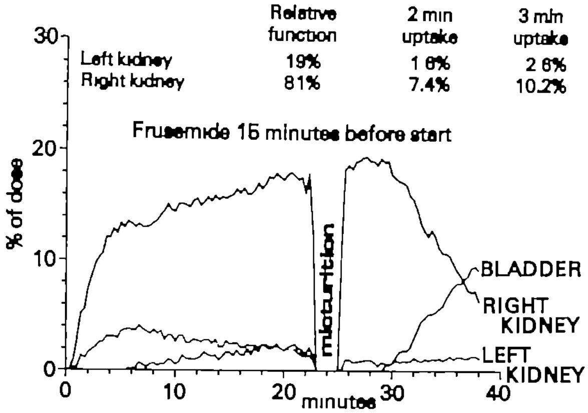
Comment

Despite its advantages in the diagnosis of upper tract obstruction (O'Reilly *et al.*, 1978), renography is unreliable in patients with a large renal pelvis or poor renal function (Kletter and Nurnberger, 1989). There is a disturbing level of disagreement between the results of renography and the Whitaker test (Whitaker and Buxton-Thomas, 1984).



	Relative function	2 min uptake	3 min uptake
Left kidney	17%	1.7%	2.8%
Right kidney	83%	9.7%	12.8%

Fig. 1 Standard diuresis renogram showing equivocal drainage from right kidney.



	Relative function	2 min uptake	3 min uptake
Left kidney	19%	1.6%	2.6%
Right kidney	81%	7.4%	10.2%

Fig. 2 F-15 renogram showing rapid drainage from right kidney after 28 min.

This case illustrates why diuresis renography may give a false diagnosis of obstruction. Renal pelvic distension occurred during the renogram until a certain point was reached when rapid drainage was initiated, suggesting a compliant but non-obstructed system. Had the test been terminated before 28 min, an incorrect diagnosis of obstruction would have been made. It is conceivable that this pattern of drainage may occur later in similar patients, in which case the 40-min "window" that renography gives us on the continuing dynamic physiological process of upper tract drainage is obviously inadequate, and an incorrect diagnosis will result.

It is suggested, therefore, that in a patient with a large renal pelvis which does not appear to have drained at the end of a standard diuresis or F-15 renogram, continued acquisition of data beyond the 40-min "deadline" may reveal drainage, as seen in this patient. It may be that in this way, the specificity of the renographic diagnosis of upper tract obstruction can be further improved.

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Requests for reprints to: G. D. Wemyss-Holden, Department of Urology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

Reverse Supine Position on Lithostar for Lower Ureteric Stones

V. BHATIA and C. S. BIYANI, *RG Stone Clinic, New Delhi, India*

Extracorporeal shock wave lithotripsy (ESWL) is now the treatment of choice for the vast majority of upper tract stones. Most lower ureteric stones can also be successfully treated by ureteroscopy. ESWL is accepted as an attractive alternative because it is non-invasive, time-saving, anaesthesia-free and easily applicable with minimal morbidity. Accurate localisation is essential for successful fragmentation.

When the patient is treated in the standard supine position on the Siemans Lithostar, the pubic bone overlaps the stone shadow in imaging with the oblique caudocranial X-ray unit (Plane II), thereby preventing accurate focusing (Fig. 1). In such a situation the reverse supine position allows easy and accurate localisation of the stone in this plane as the axis of the pelvic outlet is parallel with the axis of the oblique X-ray unit (Fig. 2).

We now treat most upper ureteric stones in the supine position, mid-ureteric stones in the prone and lower ureteric stones in the reverse supine position.

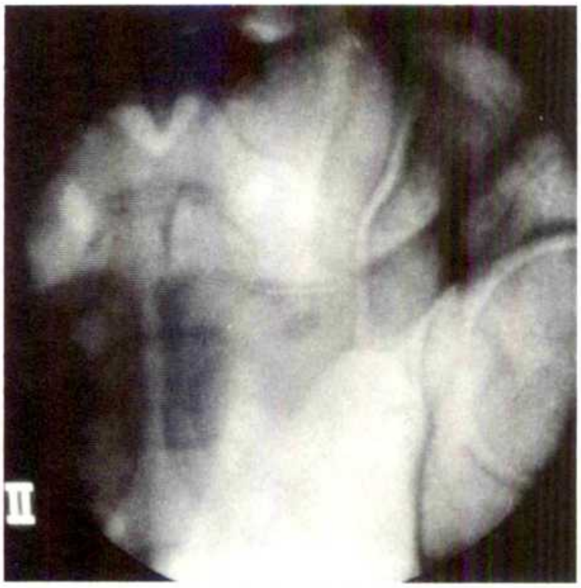

Fig. 1 Pubic bone overlap in standard supine position.

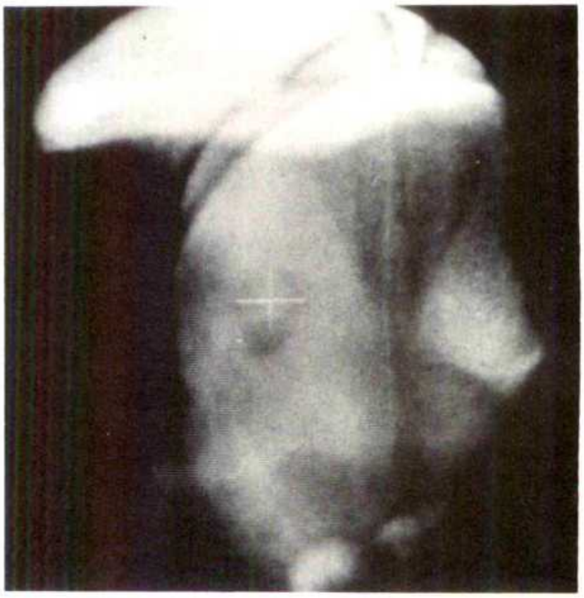

Fig. 2 Same stone in reverse supine position.

Requests for reprints to: C. S. Biyani, RG Stone Clinic, F-12 East of Kailash, New Delhi 110 065, India.

Referee's Comment

This technique is useful not just for lower ureteric stones but also has a place for ureteric stones at a level between the fourth and fifth lumbar vertebrae and also in the situation when renal stones are obscured by bowel gas.

Orchiopexy: Neo-gubernaculum Technique

O. P. SUDRANIA, *Madan-Ganga Nursing Home, Siliguri, India*

This technique deals mainly with fixation of the testis, assuming that mobilisation has been carried out satisfactorily. The essence of mobilisation of the spermatic cord (funiculolysis) lies in freeing the spermatic vessels from the triangular ligament of Denis Brown as far proximally as possible through the internal inguinal ring, retroperitoneally high up along the posterior abdominal wall. The deep inguinal ring is opened up with a Langenbeck's retractor and both blunt dissection with a pledget on an artery forceps and sharp dissection with scissors are required to free the spermatic vessels.

An incision is made along the lower inguinal crease. With the appropriate size of Langenbeck's retractor the scrotal neck is opened up, through which the index and middle fingers are inserted into the rudimentary scrotum. The scrotum is dilated by gently spreading the fingers apart a few times and at the same time slowly pushing them downwards towards the fundus of the scrotum. The fibro-fatty tissue is usually avascular but occasionally a small bleeding point may need coagulation.

The fingers are replaced with Allis forceps which grasp the dartos muscle at the fundus of the scrotum. This may need to be aided with the fingers of the operator's other hand. While maintaining gentle downwards and forwards traction on the retractor, the forceps are slowly withdrawn, inverting the scrotum so that the dartos muscle is clearly visible through the incision (Fig. 1). The dartos muscle alone is sutured with 2/0 chromic catgut to the remains of the gubernacular tissue at the lower pole of the testis with one simple stitch (Fig. 2). Care is taken to spare the skin from inclusion in the suture. The forceps and retractor are both withdrawn. The scrotal skin is pinched and pulled downwards, bringing the testis with it in the scrotal pouch (hence the term "neo-gubernaculum technique").

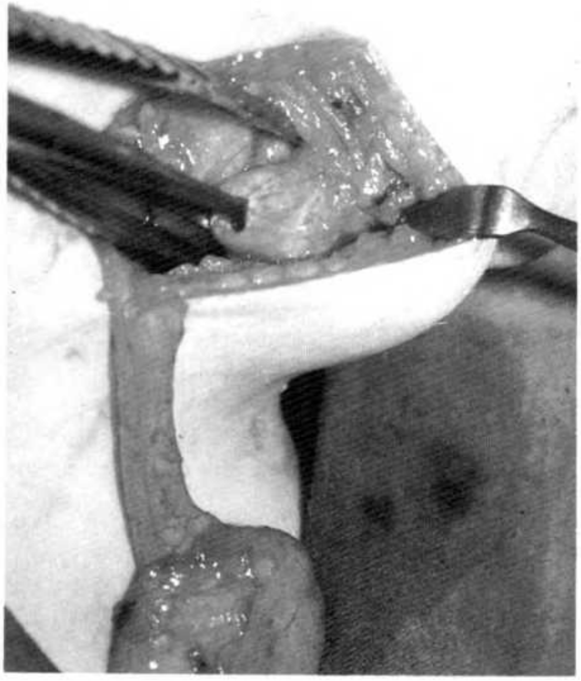

Fig. 1 Dartos muscle seen through the incision.

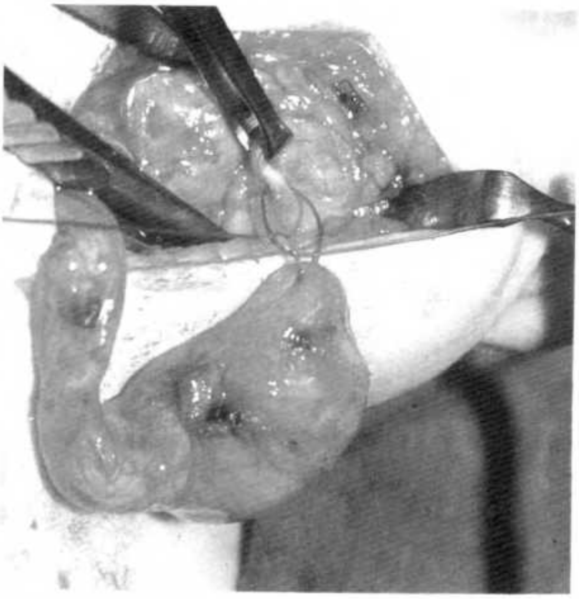

Fig. 2 Gubernacular remnants at the lower pole of the testis stitched to the dartos muscle.

The wound is closed in layers and steristrips applied to the skin. A final check is made to ensure that the eversion has been carried out and that the testis lies in the scrotal pouch. The child is mobilised when ready and after 24 hours' observation he is allowed home, with further care being entrusted to the district nurse and family doctor.

The dull, yellowish, fibro-fatty tissue must be meticulously cleared from the pearly-pink, glistening dartos muscle at the fundus of the scrotum. If the gubernacular tissue is sutured to the fibro-fatty tissue, it may result in failure of the testis to remain in the scrotal pouch.

Requests for reprints to: O. P. Sudrania, 152 Milanpalli, Station Feeder Road, Siliguri – 734405, West Bengal, India.

One-step Dilatation of the Corpus Cavernosum by Cardiac Valve Dilators

Y. VARDI, B. MOSKOVITZ and D. R. LEVIN, *Department of Urology, Rambam Medical Center, Technion-Israel Institute of Technology, Haifa, Israel*

Advances in our understanding of the structure and function of the components of the penis permit direct approaches to erectile dysfunction. The insertion of an implantable device requires gentle dilatation of the corpus cavernosum by dilators (Hegar or Pratt) to achieve diameters of 8 to 13 mm.

We suggest the use of either a De Bakey valve dilator or a Tubbs dilator in order to avoid repeated dilatations in complicated corpora (Figs 1 and 2). Our experience in 12 patients indicates that these dilators are effective and safe in those complicated cases where the corpora are narrow or affected by cavernous fibrosis. One-step dilatation reduces the risk of perforating the tunica albuginea or the septum between the corpora cavernosa and also lessens the risk of damaging the urethra (Nielsen and Bruskewitz, 1989). The curve of the dilator fits the curve of the corpora well and 1-step dilatation shortens the time needed to perform the procedure.

These 2 dilators were designed originally for transventricular dilatation of the mitral valve. They have a diameter of 7 mm when the blades are closed and dilate to 30 mm or 45 mm when the blades are fully apart. The handle includes a built-in expansion control which ensures accurate measurement of the extent of dilatation.

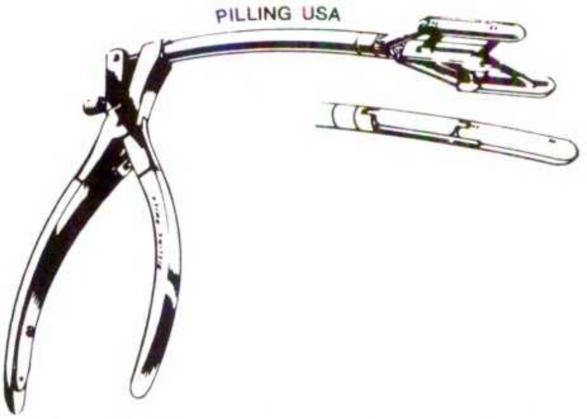

Fig. 1 Tubbs dilator for transventricular dilatation of the mitral valve.

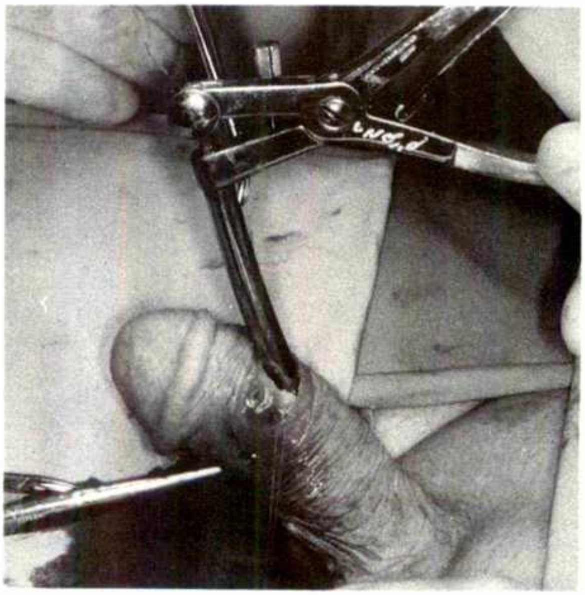

Fig. 2 Intra-operative dilatation of the corpus cavernosum using the Tubbs dilator.

Reference

Nielsen, K. T. and Bruskewitz, R. C. (1989). Semirigid and malleable rod penile prostheses. *Urol. Clin. North Am.*, **16**, 13–23.

Requests for reprints to: D. R. Levin, Department of Urology, Rambam Medical Center, Haifa 31096, Israel.

British Journal of Urology (1992), 69, 553

Correspondence

Dear Sir,

re **A comparison of aspiration, antazoline sclerotherapy and surgery in the treatment of hydrocele.** J. U. Roosen *et al. Br. J. Urol.*, **68**, 404–406, 1991.

In a randomised study the authors state that sclerotherapy should be the first choice of treatment for previously untreated hydrocele, although their group of patients undergoing surgery had superior results (no recurrence, only 1 haematoma).

Looking through this report, it appears that 85.4% of the patients had more than 1 treatment for hydrocele and even after 3 or 4 treatments 11.4% developed recurrences. Also, if the authors had adopted sclerotherapy as a first choice, 72.5% of the patients would have needed a second or third session–a very uncomfortable experience for them. Compared with our recurrence rate of 4.3% after only 1 operation in patients treated by Lord's procedure (Albrecht *et al. Br. J. Urol.*, **68**, 187–189, 1991), this outcome appears unsatisfactory.

A second weak point seems to be the statement that patients still wishing to procreate should be excluded from sclerotherapy until further studies have excluded the possible mutagenic effect of the procedure–but the study included a 19-year-old patient!

In our opinion, this study by Roosen *et al.* supports the argument in favour of surgery in the treatment of hydrocele, since more than 90% of patients can be cured by only 1 operation and since it is possible to operate under local anaesthesia on high risk patients.

Yours faithfully,

W. Albrecht and W. Höltl
Department of Urology, Rudolfstiftung, Vienna, Austria

Reply from Dr J. U. Roosen. In our series 31/35 patients (89%) were cured by sclerotherapy and 16/16 (100%) were cured by operation. These numbers are not significantly different ($P=0.42$, Fisher's exact test). None of our sclerotherapy patients needed either sick leave or admission to hospital, whereas the surgically treated patients had a minimum of 1 week's sick leave and a mean of 2.5 days in hospital. We thus feel that our conclusion in favour of sclerotherapy is consistent with our results.

According to our protocol, all adults (*i.e.* those above 17 years of age) were included. Only following the results of our study did we decide to recommend that patients still wishing to procreate should be excluded from sclerotherapy. This was based on the hypothetical possibility of a mutagenic effect from the procedure.

We thank you for having drawn attention to this matter.

British Journal of Urology (1992), **69**, 554

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth, 21–26 June 1992

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Scholarships for Experimental and Clinical Research in Urology

The European Association of Urology and the European Board of Urology will award three scholarships for research in Urology. Each scholarship will be awarded for one year, starting on 1 July 1992, at a maximum of 33,000 ECU at any appropriate institution in the world. Further information from: The European Board of Urology Education Committee, P.O. Box 25285, 3001 HG Rotterdam, The Netherlands. Tel: 31.10.436.6665. FAX: 31.10.436.6669.

Edinburgh Urological Festival

Edinburgh, 24–27 August 1992

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.

Shackman Travelling Fellowship 1993

Applications are invited from Medical Practitioners registered in the United Kingdom who are either trainees in Urology or Organ Transplantation or Consultant Urological Surgeons or Consultant Surgeons with a major commitment to transplantation of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for application is 1 September 1992.

Further particulars and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB2 9AG.

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Diary

1992

June 4–5	Second International Workshop and Symposium on New Urological Technology. Leuven, Belgium. Contact: Prof. Dr L. Baert, Department of Urology, Brusselsestraat 69, 3000 Leuven, Belgium. Tel: 016-21 75 32.
June 4–6	Fourth International Meeting of Andrology, Bellagio, Italy. "Treating Male Infertility: New Possibilities". Contact: Dr G. M. Colpi, I.S.E.S., via Vincenzo Monti 52, I-123 Milan, Italy.
June 10–12	Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.
June 22–25	Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
June 23–26	BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
July 5–12	ALASKA '92—CRUISE THE INLAND PASSAGE—Breast Imaging at Sea. Contact: ALASKA 92—Breast Imaging at Sea, Medical Seminars International, Inc., 18981 Ventura Blvd, Suite 303, Tarzana, CA 91356, USA.
July 12–19	ALASKA '92—CRUISE THE INLAND PASSAGE—Magnetic Resonance Imaging-Musculoskeletal Imaging at Sea. Contact: ALASKA 92—Magnetic Resonance Imaging at Sea, Medical Seminars International, Inc., 18981 Ventura Blvd., Suite 303, Tarzana, CA 91356, USA.
July 22–25	European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
August 2–5	International Society for Dynamics of the Upper Tract. Ninth Meeting. Akita, Japan. Contact: Dr B. L. R. A. Coolsaet, Klina Hospitals, Campus St Jozefziekenhuis, 2950 Kapellen, Antwerp, Belgium.
August 7–9	Ninth Meeting of International Society for Dynamics of the Upper Urinary Tract. Akita, Japan. Contact: Dr Seigi Tsuchida, Department of Urology, Akita University School of Medicine, 1-1-1 Hondo, Akita, 010 Japan. FAX 81-188-36-2619.
August 24–27	Edinburgh Urological Festival. Edinburgh. Contact: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.
August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
August 24–27	VIIth International Symposium on Urolithiasis and Related Clinical Research. Cairns, Australia. Contact: Dr Rosemary L. Ryall, Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia 5042.
August 30–September 4	Ninth Congress of the International Pediatric Nephrology Association. Pediatric Urology Section. Jerusalem, Israel. Contact: Dr Amicur Farkas, Department of Urology, Shaare Zedek Medical Center, P.O.B. 3235, Jerusalem 91031, Israel.

August 31	Workshop in Sacral Anterior Root Stimulation in Spinal Cord Injured Patients. Halifax, Nova Scotia, Canada. Satellite meeting of International Continence Society, September 1–4. Contact: Professor E. P. Arnold, Department of Urology, Christchurch Hospital, Christchurch, New Zealand.
September 3–6	Tenth World Congress on Endourology and ESWL, Singapore. Contact: Secretariat, c/o Department of Urology, Singapore General Hospital, Outram Road, Singapore 0511.
September 14–18	Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.
September 15–18	Euro-American Conference on Urological Cancer—Clinical and Biological Progress. Athens, Greece. Contact: Erasmus Conference Centre, International Congress Organizers, 227—229 Kifissias Avenue, Athens 145 62, Greece.
September 17–18	Seventh Annual Paediatric Urology Course. Selwyn College, Cambridge. Contact: Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
September 21–23	VIII Andrology Course. Barcelona, Spain. Contact: Secretaría General, Fundación Puigvert, c/. Cartagena 340–350, 08025 Barcelona, Spain. Tel: 34.3 2355614. Fax: 34.3 4559938.
October 1–2	Continuing Medical Education and Training in Europe: the Future. London. Contact: Dr M. W. N. Nicholls, Conference Office, c/o Fellowship of Postgraduate Medicine, 6 St Andrew's Place, London NW1 4LB. Tel: (44) (0)71 935 5556. Fax: (44) (0)71 224 3219.
October 1–3	Annual Meeting of the Swiss Society of Urology. Leysin, Switzerland. Contact: Prof. Dr P. Graber, Clinique de Chirurgie Urologique, Hôpital cantonal, CH-1211 Genève 4, or Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich.
October 1–3	Fourth World Congress of VideoUrology. Monte Carlo, Monaco. Contact: Convergences—VideoUrology '92, 120 Avenue Gambetta, 75020 Paris, France. Telex: 216 911 F. Fax: (33-1) 40 31 01 65.
October 7–11	1992 Duke Urologic Assembly. "Contemporary Issues in Urology". Pinehurst, North Carolina. Contact: Linda Mace, Assembly Coordinator, Box 3707, Duke
October 9–10	BAUS Autumn Meeting, Swansea. Contact BAUS Office.
November 1–4	Third International Workshop on Carcinoma *in situ* and Cancer of the Testis. Copenhagen, Denmark. Contact: Workshop Secretariat, c/o Professor N. E. Skakkebaek, University Department of Growth and Reproduction, Section 5064, Rigshospitalet, 9 Blegdamsvej, DK-2100, Copenhagen, Denmark.
November 8–10	Fourth International Conference of the Society for Minimally Invasive Therapy. Dublin, Ireland. Contact: Professor J. Fitzpatrick, 47 Eccles Street, Dublin 2, Ireland. Tel: +353-1-308530. Fax: +353-1-300345.
November 27–28	International Postgraduate Course on Reconstructive Surgery of the Lower Urinary Tract in Children. Amsterdam, The Netherlands. Contact: Conference Secretariat, Bureau PAOG Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands: Tel: +31 20-566 4801. Fax: +31 20-696 3228.
December 4–5	Eighth International Steglitz Paediatric Surgical Congress. Berlin, Germany. Contact: Dr F. Schier, Kinderchirurgie, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (030) 798 4181 or 798 2909; Fax: (030) 798 4141.

British Journal of Urology (1992), **69**, 557–560

Book Reviews

Complications of Urologic Surgery. Prevention and Management. Second edition. Edited by R. B. Smith and R. M. Ehrlich. Pp. xxiii + 669. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: Saunders. 1990. Price: £61.00; US$85.00.

This book is dedicated to David Jean deKernion, who died aged 17, in 1987, and is prefaced by a memorial poem called "A Thought", written by David deKernion.

The editors and their 69 contributors have completely rewritten the first edition, published in 1976, and are to be congratulated on producing a comprehensive, authoritative and up-to-date account of the complications of urological surgery, including anaesthetic, cardiac, haematological, metabolic, nutritional and pulmonary ones, together with the means of preventing them or of treating them successfully if they do occur. Each chapter is expertly written, well illustrated and accompanied by references that vary in number from 30 to 155.

As the preface says, this is a reference book, but all urologists, trained and in training, will find much of interest and value in its pages.

Current Genitourinary Cancer Surgery. Edited by E. D. Crawford and S. Das. Pp. xviii + 699. Philadelphia, London: Lea & Febiger. 1990. Price: £87.35.

The editors, together with 81 contributors, have updated and enlarged the contents of Genitourinary Cancer, which was published in 1982, to include all of the new developments that have occurred since then in the assessment and treatment of genitourinary cancers, which account for no less than 25% of all cancers in the USA.

Chapter 1 is strangely isolated from the rest of the book; it is entitled "An anatomic approach to the kidneys and retroperitoneum" and says things about the transversalis fascia that this reviewer was never taught. Chapter 2 is a very brief account of surgical diseases of the adrenal glands and the incisions available to expose the gland. Like Chapter 1, this chapter seems divorced from the rest of the book, which is excellent.

The first 2 chapters are succeeded by 9 sections, each of which considers a particular cancer or the cancers of a particular organ, beginning with a brief but comprehensive overview or summary of the pathology, imaging, staging and treatment, and continuing with detailed accounts of the appropriate operations, including percutaneous and endoscopic ones. There then follow sections on chemotherapy, radiation, ancillary procedures, and finally one on the medial and psychiatric aspects of cancer.

This book is recommended to all who seek an up-to-date and comprehensive account of genitourinary cancers and their treatment.

Current Medical Diagnosis and Treatment. 30th edition. Edited by S. A. Schroeder, M. A. Krupp, L. M. Tierney, Jr. and S. J. McPhee. Pp. 1275. London: Prentice-Hall International Inc. 1991. Price: £33.80.

This is a remarkable book—a fascinating reference source if you feel that what you learned as a resident is now a little distant. This probably applies to anyone who left medical school more than 5 years ago. This is the thirtieth annual edition and it incorporates drug information and bibliographies up to May 1990, an annual update on AIDS, new information on infectious diseases and antibiotics, new chapters on medical genetics as well as extensive revisions. It is also a useful source for the quotation by Sir Robert Hutchison—always a timely warning for everyone in the medical profession. "From inability to let alone; from too much zeal for the new and contempt for what is old; from putting knowledge before wisdom, and science before art and cleverness before common sense; from treating patients as cases; and from making the cure of the disease more grievous than the endurance of the same, Good Lord, deliver us."

Neuropathic Bladder in Childhood. (Clinics in Developmental Medicine No. 111). Edited by M. Borzyskowski and A. R. Mundy. Pp. 115. Oxford: Blackwell Scientific Publications. 1990. Price: £16.00.

This book aims to cover comprehensively all aspects of the management of the neuropathic bladder in the paediatric age group. Thus the authors are paediatricians, a clinical psychologist, urologists, a paediatric neurologist and a nephrologist. This novel approach to this subject is well planned and brings together a perspective of all aspects of the management of these children. This book also brings together clear presentations on the recent developments that have arisen from a better understanding of pathophysiology and a better understanding of alternative treatments. Undoubtedly, the introduction of clean intermittent self-catheterisation has transformed the management plan for the child with a neuropathic bladder. This book comprises only 115 pages; it is easy to read, up to date and strongly recommended to all urologists.

Advances in Urology. Volume 3. Edited by B. Lytton, W. J. Catalona, L. I. Lipshultz and E. J. McGuire. Pp. 218. Chicago, London, Boca Raton, Littleton: Year Book Medical Publishers. 1990. Price: £50.00.

As noted in the preface, the third volume of Advances in Urology focuses on some of the exciting developments in the basic sciences that have already had or will soon have a direct impact on clinical practice. The 10 topics selected for this volume are medical management of benign prostatic hyperplasia, transrectal ultrasound, an overview of polycystic kidney disease and acquired cystic kidney disease (neoplasia in disguise), oncogenes and antioncogenes in genitourinary malignancies, interstitial cystitis, failure of operations for stress incontinence, paediatric and adolescent varicocele, Peyronie's disease, radiology of impotence, and nerve-sparing modifications of retroperitoneal lymphadenectomy.

The books in this series provide authoritative reviews of well selected topics and are highly recommended for urological libraries.

Recent Advances in Urology/Andrology, Number 5. Edited by W. F. Hendry. Pp. xii + 236. Edinburgh, London, Melbourne, New York, Tokyo: Churchill Livingstone. 1991. Price: £29.95.

The continuation of this series is most encouraging. Books of this type are under severe pressure from competition in the form of review articles in journals, other specialist series, other "Advances" and "Annuals" and similar books.

For the cost-effective addict there are 15 chapters and the book costs £29.95. So is there a benefit? The answer is definitely yes and the reasons are not just patriotic, but it is important that urological literature should reflect the different emphasis and perspectives in different countries. Urology has changed rapidly. The need to include Andrology in the title of this series (after the second volume) was an indication of this. Readers will enjoy the splendid review articles that fill the book. Name almost any current topic or issue—it is here and very well presented.

Adult and Pediatric Urology. Volumes 1 and 2. Second edition. Edited by J. Y. Gillenwater, J. T. Grayhack, S. S. Howards and J. W. Duckett. Pp. 2366. St Louis, Baltimore, Boston, Chicago, London, Philadelphia, Sydney, Toronto: Mosby Year Book. 1991. Price: £184.00 for the set of 2 volumes.

The appearance of a second edition only 4 years after the first is a strong indication of the success of these outstanding 2 volumes; it also indicates the rapid changes in medical information. The editors claim to have had most of the chapters written less than a year before publication and this is an impressive achievement. To cope with future needs to keep up to date, an annual supplement in a reorganised form of the Year Book of Urology is planned.

The speed with which the material has been assembled has not led to any loss in quality or style. A reviewer, faced with 2366 pages and 2 weighty volumes, can only select certain areas of interest to look at in detail. An alternative is to see how this book handles some queries in recent practice, *e.g.* ductal cancers of the prostate—these are well covered under "Unusual prostate tumors"; actinomyces of the kidney—while certainly rare, there is no trace of a reference to this; the haematuria/loin pain syndrome—this could not be traced in the index; interstitial cystitis—this is covered by a useful summary that carefully avoids some recent controversies.

It is tempting to expect that these volumes are encyclopaedic—they are certainly comprehensive but, as Dr Gillenwater says in his Preface, excessive detail has been avoided to keep the text readable and user friendly.

Some small quibbles. The editors doggedly keep to "excretory urography" but surely "intravenous urography" and its popular abbreviation are now preferred. The spelling of "calix" for "calyx" can still be debated, though the former is etymologically preferred. It is disappointing that urologists have not been able to achieve an acceptable international uniformity of terms for staging tumours.

These 2 volumes have clearly taken this publication to the pole position among competitors in the big book-of-urology race. If the standards are maintained, these books will easily hold that position.

Tumors and Tumor-like Conditions of the Kidneys and Ureters. (Contemporary Issues in Surgical Pathology, Volume 16). Edited by J. N. Eble. Pp. xiii – 268. New York, Edinburgh, London, Melbourne: Churchill Livingstone. 1990. Price: £40.00.

The flow of books on urological pathology continues unabated. There are now several major textbooks on the subject, as well as monographs on individual topics, *e.g.* bladder and prostate. We now have a well produced volume on tumours of the kidney and ureter with 17 contributors from North America and Europe under the editorship of Dr J. N. Eble. This is a timely production since, as the Editor points out in the Preface, Bennington and Beckwith's monograph was published in the 1970s and there have been major advances in our knowledge and understanding of the subject since that time.

This certainly applies to renal tumours of childhood and this subject is well covered, at least for the non-specialist in paediatric pathology. The chapter on unusual renal tumours is useful and the references are particularly helpful. There are also welcome reviews on immunohistochemical findings and DNA analysis of renal tumours. Renal adenocarcinoma is well covered and includes discussions on the problems of tumour grading and the significance of tumour size in assessing behaviour and prognosis. A minor criticism of this chapter might be that discussion of oncocytomas and renal cell carcinomas composed of granular cells is a little confusing.

A clearer and more detailed description and review of oncocytic tumours of the kidney would have been helpful. The only reference to oncocytoma in the index refers to animal models. Incidentally, there is a thorough review of experimental renal tumours.

All in all, this is a most welcome publication and a valuable addition to the medical library and to the personal collection of any surgical pathologist with an interest in the subject.

Orgasm—New Dimensions. By P. Kothari. Pp. 144. Bombay: VRP Publishers. 1989. Price: US$75.00.

The author, as Professor of Sexual Medicine, has hosted the First International Conference on Orgasm. The book reminds us of how confused the clinical scene is in regard to this aspect of sexual behaviour.

The first section of the book comprises a useful guide through the multiple nomenclatures that abound in clinical practice when a subject such as this is poorly understood. The author presents a relatively simple system of classification which, if more commonly adopted, might allow comparison of results to be more readily achieved.

The second section deals with sexual grounding and stresses its importance. This is a timely reminder for all those whose interests and management of sexual difficulties extend no further than a narrow focus on the end organ and injections, of the interplay between desire and physical responses.

Multiorgasm is unlikely to constitute a major clinical problem. The author describes physical changes recorded (EEG, ECG, *etc*) in 2 females and 1 multiorgasmic male. He feels for the male it is the "outcome of effort but for the female it is an effortless experience". This section is the least successful of the three.

Most urologists will gain little of immediate practical help from the book, although the andrologist should find the review of the topic helpful.

Essentials of Uroradiology. By E. S. Amis, Jr. and J. H. Newhouse. Pp. xiv + 427. Boston, Toronto, London: Little, Brown and Co. 1991. Price: £55.00.

It is not often that one comes across a radiological text which has more than a passing relevance to another clinical discipline. This book, written exclusively by 2 radiologists, proves the rule. It has been compiled with 2 specific groups in mind, namely trainee radiologists and trainee urologists. As a valuable radiological reference it undoubtedly succeeds, and it could prove to be invaluable to the budding urologist.

Its strength lies in the authors' ability to put current imaging strategically into the clinical context of urology. The 427 pages of tightly packed, highly relevant information are supported by superb line drawings and quality images that represent all modern modalities, including MRI. Embryology, aetiology and pathology are skilfully integrated with imaging strategies and, where relevant, management philosophy. Growth points, including urodynamics, impotence and male infertility, are concisely reviewed and complement the more traditional areas of urological practice. Paediatric urological problems are included to complete the overview. The bibliography is extensive and up-to-date.

This book is thorough, practical and very easily read. It is unlikely to collect much dust on the shelves of imaging department libraries and it is commended unreservedly to urologists in training.

Long-term Paediatric Urology. By C. R. J. Woodhouse. Pp. 215. Oxford: Blackwell. 1991. Price: £49.50.

Paediatric urologists like to believe that most of their patients are being offered the possibility of surgical cure. But is this belief misplaced? How real is the legacy of late morbidity? And how many apparent surgical triumphs turn sour in adult life? For the paediatric urologist these are important questions. No-one is better qualified to provide the answers than the author of this book.

Drawing on his extensive experience in this field, Mr Woodhouse has also undertaken a painstaking review of the literature. The first chapters deal with the mechanisms and management of late renal failure, including transplantation into an abnormal lower urinary tract. Reviewing the late outcome of procedures such as pyeloplasty and ureteric reimplantation, the book examines such topics as the late risks of hypertension, complications in pregnancy and the management of reflux in adults.

Reconstructive urology is represented by a number of important chapters. Exstrophy and epispadias and the management of erectile deformities are considered in detail. Reviewing the late outcome of urinary diversion and enterocystoplasty, the book considers not only the functional results but the possible potential for late malignant change. The chapter on posterior urethral valves exemplifies the need for careful long-term surveillance of children operated upon in infancy.

Less informative perhaps are the sections on hypospadias and the undescended testis. Hypospadias surgery divides into 2 eras, before and after Duckett. In a book of this nature it is inevitable that the chapter on hypospadias will deal largely with outdated procedures. Anyone who has attempted to study the literature on the later outcome of orchiopexy, fraught with anecdote and contradiction, will appreciate this thoughtful analysis of a difficult subject.

This is an important book which will be valued not only by paediatric specialists but by any urologist who is called upon to operate on children.

Diagnosis and Management of Impotence. By A. W. Zorgniotti and E. F. Lizza. Pp. xiii + 173. Philadelphia: Decker. 1991. Price: £46.00; US$69.00.

The authors of this book have been at the forefront of the recent advances in the management of impotence. Their latest contribution is a beautifully presented and clearly written guide to the diagnosis and management of impotence and should be required reading for all those involved in the management of this condition. Radiologists, sex therapists and urologists will all benefit from the logical and sensible approach described.

The radiographs are clear and easy to interpret and the drawings for the sections on operative surgery are outstanding. The references are adequate and up-to-date.

A book review serves several purposes, including the improvement of subsequent editions. It is a pity that there is no section on penile implants. In describing the surgical treatment for veno-occlusive dysfunction, it is unlikely that the exposure described by the authors could be achieved without separating the corpora from the pubis.

This is a most enjoyable book and is thoroughly recommended.

Infertility in the Male. Second edition. Edited by L. I. Lipshultz and S. S. Howards. Pp. xii + 468. St Louis, Baltimore, Boston, Chicago, London, Philadelphia, Sydney, Toronto: Mosby Year Book. 1991. Price: £60.00.

This is the second edition of a textbook edited by 2 distinguished North American urologists/andrologists. It benefits not only from the correction of deficits in the first edition but also because new knowledge has been incorporated. This means that it is worth making the investment to buy this book, since it contains state-of-the-art chapters on all aspects of male infertility. A minor criticism is that the chapters by different experts make it slightly difficult for the busy clinician to find guidance about some particular problems, as several different chapters may have to be consulted. Nevertheless, this book can be recommended to all departments where there is an interest in male infertility.

Magnetic Resonance Imaging of Carcinoma of the Urinary Bladder. (Series in Radiology, Volume 21). Edited by J. O. Barentsz, F. M. J. Debruyne and S. H. J. Ruijs. Pp. xi + 121. Dordrecht, Boston, London: Kluwer Academic Publishers. 1990.

This book confirms that magnetic resonance imaging (MRI) is the best modality currently available for staging bladder cancer. In a review of the world literature, however, the number of patients reported with bladder cancer investigated by MRI is relatively few. The considerable experience of the authors in this field is outlined in a clear, concise and easily readable form. The general principles of MRI are introduced and the best pulse sequences for imaging bladder cancer are described. Results achieved with a weaker magnetic field (0.5T) are compared with those obtained with a stronger field (1.5T) and the influence of a surface coil on image quality is also evaluated. Magnetic resonance images of the normal male and female pelvis are well illustrated to provide a comparative baseline or reference point for patients with bladder cancer. A chapter is devoted to reporting the authors' comparative study of MRI with computed tomography with reference to cystectomy and autopsy specimens. For superficial disease the reference point was clinical staging with 9-month and 3-year follow-ups.

This book is well produced. It has excellent illustrations and can be recommended as a valuable reference book for all concerned with the diagnosis and management of bladder cancer.

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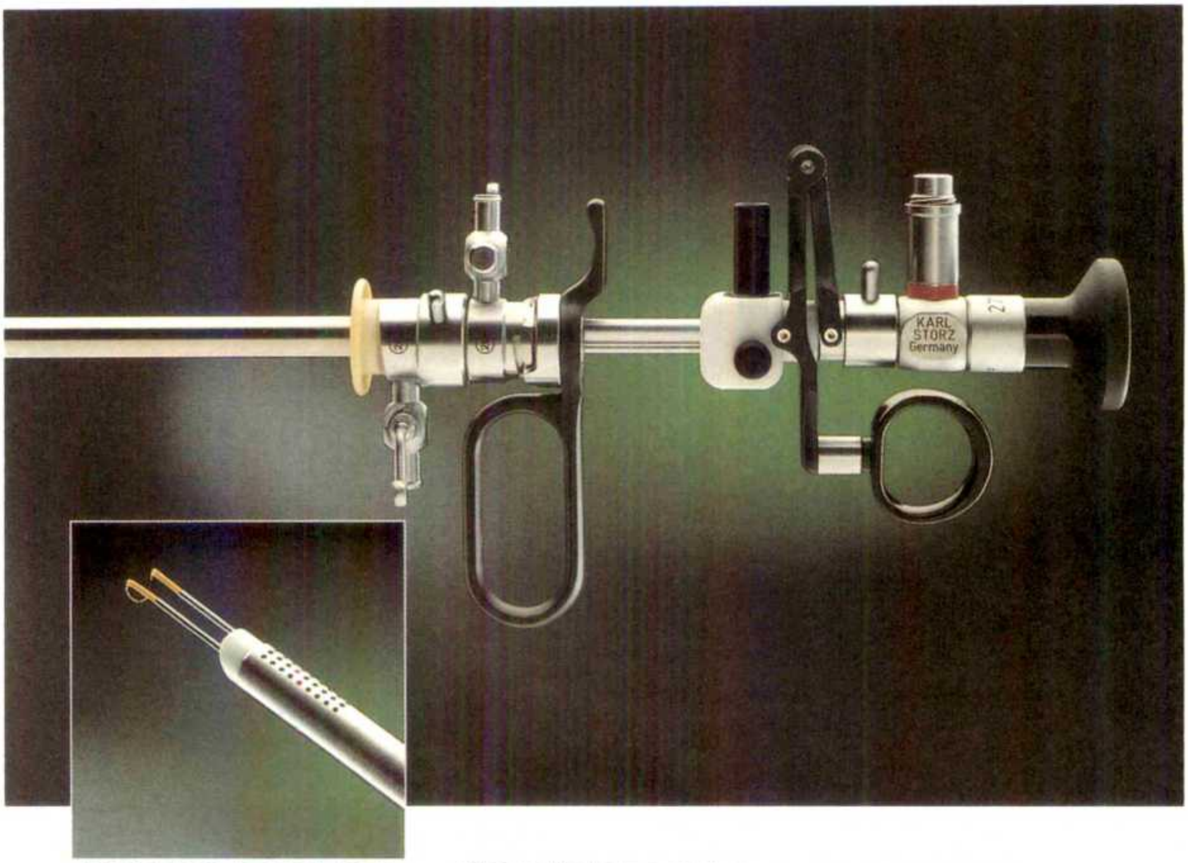

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REVIEW

Laparoscopy in Urology: Perspectives and Practice

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Laparoscopic techniques are transforming general surgery and general surgeons and the same revolution is about to occur in urology. Laparoscopy has been previously regarded as an interesting clinical diagnostic tool with very few applications. It has been well documented that laparoscopy can be helpful in localising impalpable undescended testes when both ultrasound and computed tomography (CT) have failed to help (Cortesi *et al.*, 1976; Malone and Guiney, 1984, 1985). However, an individual urologist sees few such cases and so the technique of laparoscopy has been very much left in the background. Laparoscopy need not be merely diagnostic. It is an operative technique and is currently being used to perform pelvic lymphadenectomy, varicocele repair and nephrectomy. Many urologists will perceive that whilst it may be feasible to carry out all of these procedures via a laparoscope it will not be without a great deal of operative time and technology overkill. This perception is not justified. One must return to the patient-priority concept of minimally invasive therapy (Wickham, 1987) and that is to achieve the ideal operative result with minimal trauma and a rapid return to normal activities for the patient. This was exemplified in King's College Hospital when a post-operative laparoscopic nephrectomy patient required only oral analgesics, was able to tolerate diet on the first operative day and went home on the third post-operative day.

This Review outlines the basic techniques of operative laparoscopy and explains in some detail the current applications in urology, which are:

1. Pelvic lymphadenectomy (prostate and bladder cancer staging).
2. Varicocele repair.
3. Nephrectomy (malignant and benign conditions).

Kelling in 1901 described a case report of inspection of the abdominal cavity of the dog using a cystoscope introduced through a small stab wound. That same author then described his use of this technique of laparoscopy in man in 1923. Jacobeus in Stockholm in 1910 reported the use of a cystoscope for examination of the peritoneal and pleural cavities. His instrument was inserted through a sheath-trocar system and both water and air were used to distend the cavity. Further details on the historical perspectives of laparoscopy can be found in the review by Gunning (1977). However, it was not until the introduction by Kalk of purpose-designed instruments that modern laparoscopy was established. His accumulated experience of over 2000 cases was published in 1951 (Gunning, 1977). Although sometimes used for staging intra-abdominal metastatic disease by general surgeons and gastro-enterologists, laparoscopy has generally been reserved for inspection of pelvic organs by gynaecologists. Limited operative techniques such as tubal clipping have been practised widely, but the more elaborate operative procedures described by Semm (1987) were practised by only a few. It is interesting to see that Semm's work, once heavily criticised by gynaecologists and general surgeons in Germany, has now been reappraised and, as the living father of this technology, his presence is in even greater demand around the world. The catalyst for this explosion of interest in operative laparoscopy must be the pioneering work of Reddick and Olsen (1989), general surgeons who undertook over 200 laparoscopic cholecystectomies when most other surgeons were still arguing over the theoretical advantages. What is difficult to explain is the very rapid acceptance of this technique by both clinicians and patients and the snow-balling effect

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amongst previously placid gynaecologists and now amongst urologists who always should have known better.

Instruments

The laparoscopic procedures mentioned above can all be performed with standard gynaecological instruments, but it is rather like undertaking a percutaneous nephrolithotomy with a cystoscope and basket. There are now specialised dissecting, grasping, retracting, cutting, clipping and stapling instruments which have made these very complicated procedures much more straightforward. There is still some way to go in the evolution of these instruments, but this will occur soon as more and more surgeons are able to impart their personal experience to the various companies. The best current instruments are disposable or, if looked upon in the same light as many of our other urological disposables, are perhaps best described as semi-disposable, since many of them will tolerate up to 3 ethylene oxide sterilisations. These disposable instruments include not only the manipulative devices but also the trocars and cannulae. If new devices are used at each procedure, the additional cost to a varicocelectomy is currently about £300 and a supplement of nearly £700 must be added to a laparoscopic nephrectomy. This is balanced by a saving in ward costs of approximately £1500 for each nephrectomy patient (3 in-patient days *vs* 8 for open surgery). These are important considerations and must be borne in mind when debating the value of these laparoscopic procedures.

The ideal portals of entry into the abdomen are made with disposable trocars and cannulae. These come in diameters of 5, 10 and 12 mm. Special safety devices are built into them that prevent underlying bowel being perforated. Scissors, grasping and dissecting instruments can be used through 5-mm ports but the larger endoscopic clip appliances and, in particular, the new endo GIA stapler from AutoSuture Company need the largest 12-mm port. The larger ports can be converted by the simple insertion of a spacer to facilitate the use of the smaller instruments. Thus many procedures use a mixture of these ports and the exact placement can be seen in Figure 1.

All operative laparoscopic procedures should be carried out from a monitor with the use of a charge coupled device (CCD). These can now be inserted directly into the end piece of a laparoscope rather than just clipped on. The present use of such cameras for transurethral surgery and other urological endoscopic operations will make the learning of laparoscopy much easier for those already experienced with these cameras. Two monitors are usually used, one placed directly opposite the main operator and the other directly opposite his or her assistant.

General techniques

The common starting point for all laparoscopic procedures is the formation of a pneumoperitoneum. The initial puncturing needle through which gas is insufflated has traditionally been called a Veress needle. This is also available as a disposable needle with the same safety mechanism as the trocars and cannulae (Yuzpe, 1990). The needle is held as a dart and pushed into the abdominal space, helped by the pulling up of a fold of the abdomen.

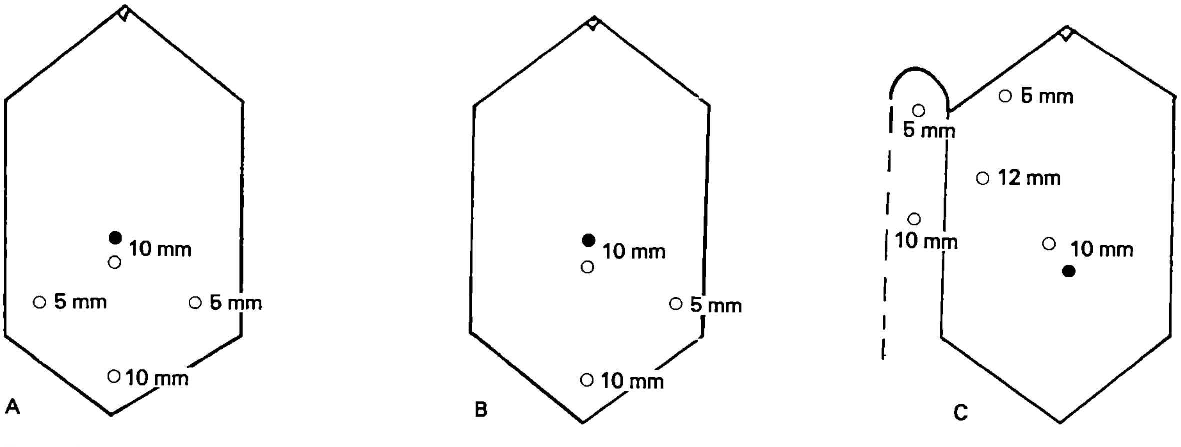

Fig. 1 Entry ports for laparoscopic procedures. (A) Pelvic lymphadenectomy. (B) Varicocelectomy. (C) Nephrectomy.

Injection of a small amount of water through the needle indicates if it is well positioned. The needle is then connected to a gas insufflator. Carbon dioxide is traditionally used to enlarge the intraperitoneal space. There have been a few reports of carbon dioxide emboli, but it is generally held to be a very safe gas (Kelman *et al.*, 1972). Nitrous oxide is occasionally used when diagnostic laparoscopy is performed under local anaesthesia because there is a much less irritating effect on the peritoneum (Marshall *et al.*, 1972). Modern insufflators not only provide varying flow rates, and a measure of the volume and pressure infused, but can also be set to an automatic mode, which is valuable during lengthy procedures. If the initial infusion pressure is above 10 mm of mercury, one must suspect that the Veress needle is not lying free within the abdomen. This is usually corrected by simple repositioning of the tip. Subsequent pressures again should not exceed 10 mm of mercury because this would severely impede the venous return through intra-abdominal organs over a period of several hours. This, however, is a theoretical concept and much work still needs to be done concerning the possible hazards of very long laparoscopic procedures. Until now we have, perhaps naively, felt that the anaesthetic risks of a long laparoscopic nephrectomy are similar to the risks involved in crossing the Atlantic in a jumbo jet, where danger arises only at the beginning and end of the procedure. Patients absorb approximately 200 ml of carbon dioxide per min, which produces a profound acidosis when a procedure lasts for more than an hour. This should be countered by measuring the end tidal carbon dioxide and altering assisted ventilation accordingly.

A 10 or 12 mm trocar and cannula is then inserted into the abdomen for initial laparoscopic viewing. This is traditionally via a small skin incision on the periphery of the umbilicus. This site has mainly been used for its cosmetic appearances and we are now finding many instances when the camera should be placed elsewhere. A golden rule to follow is that the viewing laparoscope, with or without its associated camera, should be inserted away from the site of operation. This provides the potential for both close-up and distant wide angle views once several instruments are in the operative field.

Laparoscopic pelvic lymphadenectomy (LPL)

This is a procedure inherently more attractive to those practising in the USA and Germany (Meyer-Burgh and Ziegler, 1978; Zincke *et al.*, 1982) because it concerns the accurate staging of prostate and bladder cancer. Our traditional and conservative management of local prostate or invasive bladder cancer has been orientated towards radiotherapy and there has been little effort accurately to stage these tumours because the nihilistic aim has been to control local disease only. Cure was an infrequent bonus. This has, in part, been due to the difficulty in staging these tumours previously, but the advent of this minimally invasive laparoscopic procedure means that we might see a trend towards accurate staging prior to definitive management. CT is accurate only when local nodal metastases are macroscopically involved (Schubert and Heidl, 1978). Although the presence of microscopic metastases in the pelvic lymph nodes is associated with only a slightly improved prognosis, any thought of cure by local treatment is unrealistic and, if found, these patients should be offered systemic therapy. They should certainly not undergo radical surgery or even radiotherapy unless one is only hoping to control local disease.

Previous attempts have been made to sample lymph nodes endoscopically by using a retroperitoneal route (Hald and Rasmussen, 1980; Dan *et al.*, 1982). This was a very haphazard technique which often sampled only very small amounts of tissue and could not be done with any great degree of confidence. The current technique of LPL (Griffith *et al.*, 1990) permits good visualisation of the node bundle in the obturator fossa and nodes right back to the junction of the external and internal iliac veins. One can achieve an almost complete lymphadenectomy from this area which, although recognised as not being curative in itself, does yield a much higher degree of accuracy in determining the presence of micrometastases.

Many presentations at the 1991 Congress on Endourology used LPL as the first choice in node-staging prostate and bladder cancer (Schmeller *et al.*, 1991; Winfield *et al.*, 1991). Despite being a minimally invasive procedure which can usually be carried out on a day-case basis, its role should be in patients who are CT-negative, because the use of CT will pick up at least those who do have macroscopic node involvement and these can be biopsied by CT-guided fine needle aspiration.

Four ports are used (Fig. 1A). The operation is best done from the opposite side. The peritoneum is picked up and incised just medial to the iliac vessels and close to the pubic ramus. The vas is identified, ligated with clips and divided. If the ends of the vas are pulled apart, the obturator space begins to open up. The peritoneal incision is extended medially until the node bundle can be observed. The node bundle can usually be removed in 1 or 2 pieces with the use of both clips and diathermy. The obturator nerve can easily be identified and left intact, but the obturator artery and vein can be divided if necessary. A bilateral lymphadenectomy takes approximately 2 h to complete. The author has undertaken 21 of these procedures and 16 patients were able to go home on the same day. Of the remaining 5 patients, 3 went home on the following day, but 1 patient went into urinary retention and subsequently required a transurethral resection of the prostate. One patient required an immediate open laparotomy when it was impossible to control a branch of the internal iliac artery by endoscopic means. This patient went on to have open lymphadenectomy. This has been the only major complication in these laparoscopic procedures. However, bleeding remains an unwanted complication. It is very difficult to mimic the use of immediate pressure or dabbing that is done at open surgery. Good endoscopic views and accurate dissection require a very clean field. At present, the speed at which a cut vessel can be picked up with forceps and clipped or diathermied is a little slower than at an open operation and it becomes more difficult when such a vessel exists within a pool of blood. It is possible to aspirate and irrigate through the laparoscope, but aspiration in particular plays havoc with the volume of gas within the abdomen and over-zealous aspiration can lead to everything collapsing around one. Microscopic metastases have been identified in 3 patients in this series and their management has been subsequently altered. One patient who would otherwise have been a candidate for a radical prostatectomy has received hormonal manipulation because even radiotherapy could not cure nodal disease and would possibly have produced unnecessary morbidity. Two patients with carcinoma of the bladder have been given radiotherapy (recognising that this is only for local control) and both will be receiving systemic chemotherapy.

Laparoscopic varicocelectomy

This procedure can be carried out through 3 ports (Fig. 1B). It is more than the equivalent of a high Palomo approach in that there is not only ligation and excision of the dilated testicular veins, but one can also remove those veins branching through the back of the inguinal canal lower down and often seen travelling with or close to the vas. It is the quickest of all laparoscopic operative procedures and can be completed within 30 to 40 min. All of our patients have gone home on the same day and there have been no complications. All of the varicoceles have been successfully treated, but the disadvantage remains in those patients in whom a testicular biopsy is also required. Such patients should probably have the more traditional low approach, when both procedures can be carried out through the same incision.

Laparoscopic nephrectomy

There was much excitement at the American Urological Association meeting in 1990 when Ralph Clayman presented his series of 4 patients; he has now treated 8 patients (Clayman *et al.*, 1991). All but 1 had undergone a successful laparoscopic nephrectomy for benign disease. He introduced the concept of dissecting the kidney laparoscopically through the peritoneal space, delivering the organ into an impermeable bag, bringing the bag neck out of the abdomen and inserting a morselating device to remove the tissue. It is his application of the bag principle that has made this operation safe and feasible. Such bags are now being used by general surgeons for "hot" gall bladders. Rassweiler and I carried out 2 laparoscopic nephrectomies in dogs in 1990, removing the kidneys with the endoscopic liquidiser and surgical aspirator (Coptcoat, 1990). However, both cases required initial embolisation and the subsequent removal of tissue was haphazard, difficult to visualise and deemed to be dangerous. Thus the use of an impermeable bag to protect other organs and allow safe blind liquidisation or morselation is an advance. The patient is placed in the lateral kidney position with the table broken. At least 5 ports are used (Fig. 1C). The lateral aspect of the colon is dissected away from the lateral wall to facilitate the introduction of ports in the mid-axillary line. This manoeuvre must be carried out first and the ports put under direct vision to prevent retroperitoneal bowel perforation. In this position lateral dissection allows the kidney to fall towards the midline. The ureter can be found, clipped and used as a retractor. Renal vein and artery clipping cannot be completed with the normal endoclips because these are not reliable for large vessels. The introduction by Auto Suture of an endo GIA instrument has solved this problem. This ingenious device places 2 rows of miniature staples across any vessel and incises between them (Fig. 2). Our first operations have been as long and tedious as those reported in the USA and the mean time taken was 5 h 15 min. This includes the time taken to manipulate the freed kidney into a bag and the subsequent tissue morselation. It is the manipulation of the kidney

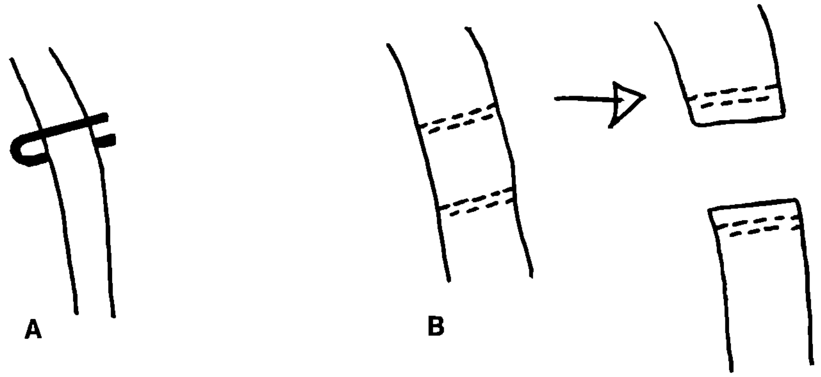

Fig. 2 Techniques for laparoscopic haemostasis. (A) Endoclips. (B) Endo GIA Stapler.

into the bag that seems to take an undue length of time but with new designs of bags the overall time of the operation will greatly decrease.

We have now carried out 6 laparoscopic nephrectomies (Table). The first, carried out with John Wickham, was for a symptomatic, dysplastic, small kidney. This was successful and prompted us to adapt the procedure for renal carcinoma. It is much easier laparoscopically to dissect around the perinephric fat rather than through it and this enables a complete radical nephrectomy with lymphadenectomy to be performed quite successfully through the laparoscope. It requires an even larger bag! Morselation within the bag can be viewed laparoscopically through an adjacent port and there is no danger of seeding cells within the abdomen. Three of our 6 patients have undergone a laparoscopic radical nephrectomy for renal carcinoma and all have been discharged home within 3 days. There has been 1 failure in our series of 5 patients so far and this concerned a large non-functioning kidney containing a staghorn calculus. There was extreme perinephric inflammation and the dissection was abandoned after 5 h because little progress was being made. Indeed open dissection was still quite difficult, as it often is in these patients with previous perinephric infection and inflammation. My tendency therefore, at present, is to apply the laparoscopic nephrectomy procedure either to renal tumours or to benign small kidneys where there has been no history of infection. The renal tumours should be either renal carcinomas stage I or II where there is no CT evidence of tumour spread outside the renal capsule or into the renal vein, or transitional cell tumours of the kidney or ureter. These can also be removed laparoscopically, but one must include the ureter in the specimen. This is not a difficult additional procedure and one can apply the technique of preliminary transurethral resection of the ureteric orifice, dissection of the ureter laparoscopically down to the bladder and the application of gentle traction. One such patient has also been successfully treated at the Institute of Urology this year.

Table Patients Treated by Laparoscopic Nephrectomy

Diagnosis	*Sex*	*Age (years)*	*Outcome*	*Operating time (h)*
Dysplastic kidney	M	26	Success	6.5
Renal carcinoma	M	58	Success	5.5
Staghorn	M	45	Failure	7.0
Renal carcinoma	M	66	Success	5.8
TCC* renal pelvis	F	72	Success (nephro-ureterectomy)	6 0
Renal carcinoma	M	75	Success	5.0

*TCC = transitional cell carcinoma.

Discussion

Operative laparoscopy is gaining momentum in many specialties. Urologists have been a unique breed of surgeons in that they have often been able to combine both innovation and a background of endoscopic training to push frontiers further and faster than any other sub-specialty. I hope that this will also apply to laparoscopy in urology. There are many other procedures which may be feasible with the laparoscope. These include the formation of an ileal conduit and possibly even a laparoscopic cystectomy. It is relatively easy to carry out a laparoscopic cystectomy in a pig, but the intraperitoneal anatomy of the pig's bladder lends itself much more favourably to this technique. Semm (1987) has described techniques for ligation and suturing via the laparoscope and these, in combination with new clipping and stapling techniques, allow almost any procedure to become feasible. We will probably see textbooks of operative procedures being completely re-written, but there will be an important feasibility stage before we eventually see the role of laparoscopy in its true perspective. By this I mean that there will certainly be some operations best done laparoscopically, but others where the over-elaboration and possible complications make it only a technical exercise. Of the current operations described above I would suggest that a laparoscopic varicocelectomy possibly constitutes an overkill, especially when one would have to make a separate incision for a testicular biopsy for varicoceles being done in infertile men. Larger series of patients need to be studied to determine this but in the meantime it at least provides an excellent training exercise for the more complicated procedures such as nephrectomy. There is no doubt that one needs to perform at least 10 procedures before feeling confident about the handling of long endoscopic manipulative instruments and their orientation on a monitor.

Laparoscopic lymphadenectomy has proved to be an excellent procedure in terms of efficacy and safety, but with the proviso that it has relevance only if the finding of micro-metastases changes the course of patient management. This may well be resolved when an answer can be gained to the question of whether chemotherapy is best undertaken before or after radical surgery. However, even traditional urologists who see the role of any lymphadenectomy as irrelevant must admit that the accurate staging of prostate and bladder cancer will improve our knowledge of the disease (MacLaughlin *et al.*, 1976; Zincke *et al.*, 1982) and, in particular, give us a better insight into the role of radiotherapy when there has been little or no attempt accurately to stage such tumours prior to treatment.

There is little doubt that laparoscopic nephrectomy is here to stay and it will become a common sight in our operating theatres. Before long it will be carried out in approximately 3 to 3.5 h. Our most recent laparoscopic nephrectomy was completed within 4 h with the use of a new bag. This is still almost twice the length of its open counterpart, but the benefits to the patient must outweigh this factor. We must canvass for more operating time even at the loss of bed numbers which have been, until now, the traditional indicators of a surgeon's status.

At present, all of my patients who are to undergo a laparoscopic nephrectomy have an arteriogram. I have not found that prior embolisation, which was undertaken in 1 patient, makes any difference, but at this stage in the development of the procedure a knowledge of the exact arterial anatomy is of great benefit. Smaller arteries (3–4 mm in diameter) can be safely ligated with multiple endoclips, but a single or double renal artery, especially when affected by arteriosclerosis, needs more secure ligation. The endo GIA stapler by Auto Suture has solved this problem and the miniature row of staples resists extreme pressures and manipulations in *in vitro* studies. This has always been a difficult part of the procedure, but the use of stapling rather than clips for such large arteries has alleviated the problem. The method used to morselate and remove the tissue from the bag is not important. In some cases we have simply inserted a pair of curved Mayo scissors into the bag and fragmented the tissue with these. Both mechanical and electrical morselating/liquidising devices are available, but the important point is that they can all be used providing there is no risk of bag perforation. The concept of an organ bag has also led me to use either a rubber glover finger or condom when collecting multiple biopsy or node specimens during any laparoscopic procedure. The total amount of material can then be brought out as one without the repeated removal of individual pieces which can often be lost within the cannulae or inadvertently crushed by the forceps.

Many of our standard operations are now being reconsidered and we may even need to reconsider or revise some of those procedures already being undertaken laparoscopically. Some centres have already described clipping of the artery into an intra-abdominal testis prior to a second-stage open orchiopexy (Castilho, 1990).

There is a great need to share laparoscopic experiences between sub-specialties and advances will be made in many hospitals where general surgeons, gynaecologists and urologists sometimes work as a team, or at least discuss their experiences. This has happened at King's College Hospital and has also helped to solve the problem of the cost of high technology. We are able to co-ordinate our procedures and share all of our equipment. Such co-operation will also be essential in training surgeons in operative laparoscopy and we hope to see the setting up of courses in the coming year.

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J-wire Facilitates Retrograde Manipulation of Ureteric Calculi Prior to Extracorporeal Shock Wave Lithotripsy

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Summary—During a 13-month period, 55 patients underwent attempted retrograde manipulation for ureteric lying above the pelvic brim. The mean stone burden was 11 mm (range 5–21); 41 stones (75%) were primary ureteric calculi and 14 (25%) were fragments resulting from extracorporeal shock wave lithotripsy to renal calculi. The method of retrograde manipulation was recorded prospectively. Retrograde flushing through an 8F angiography catheter with a mixture of saline and lignocaine gel was successful in 27 patients (49%). The insertion of a J-wire through the angiocath allowed for successful manipulation in a further 17 patients (31%). Retrograde manipulation was impossible in 11 patients (20%). There were 4 complications (7%), none attributable to the use of a J-wire.

Dissatisfaction with the results of *in situ* treatment of upper ureteric calculi by extracorporeal shock wave lithotripsy (ESWL) has led to the introduction of retrograde manipulation of calculi into the renal pelvis prior to ESWL. Chadbourne and Lyon (1988) described retrograde flushing of ureteric calculi by injecting 2% lignocaine gel through an 8–10F angiography catheter placed just distal to the stone. They report a 94% success rate in a series of 47 patients treated by this technique.

Our initial experience with retrograde flushing of ureteric calculi was less successful. However, we found that when flushing failed to dislodge calculi, the introduction of a J-wire through the angiocath frequently allowed for successful retrograde manipulation. More recently, we have recorded prospectively the techniques which have been used to dislodge ureteric calculi.

Patients and Methods

Between July 1989 and August 1990, 55 patients underwent attempted retrograde manipulation for ureteric calculi lying above the pelvic brim. Their mean age was 54 years (range 18–78). An intravenous urogram had been carried out in each case, providing definition of the ureteric anatomy. There were 44 primary ureteric calculi and 11 fragments caused by ESWL to renal calculi. Fifty patients had single ureteric calculi and 5 had multiple. Six patients had undergone unsuccessful *in situ* ESWL to ureteric calculi prior to attempting retrograde manipulation.

Under general anaesthesia a straight floppy tipped guide wire was advanced to just below the level of the ureteric calculus. An 8F angiocath was inserted over the guide wire, which was then removed. A 1:2 mixture of 2% lignocaine gel and 0.9% saline was used for flushing. Initially 10 to 20 ml were injected. If this was unsuccessful, an attempt was made to advance the angiocath past the calculus and to inject a further 2 to 3 ml for lubrication beyond the stone. After waiting for a few minutes a second attempt was made to flush the calculus. If this also failed, a J-wire was inserted through the angiocath and a further attempt made to dislodge the stone. As the curved tip of the J-wire was advanced it often "hooked" the calculus (Fig.), which was then deflected backwards by a series of short sharp movements. Axial rotation of the J-wire sometimes facilitated coupling of the curved tip with the stone if the first pass had been unsuccessful. The procedure was monitored

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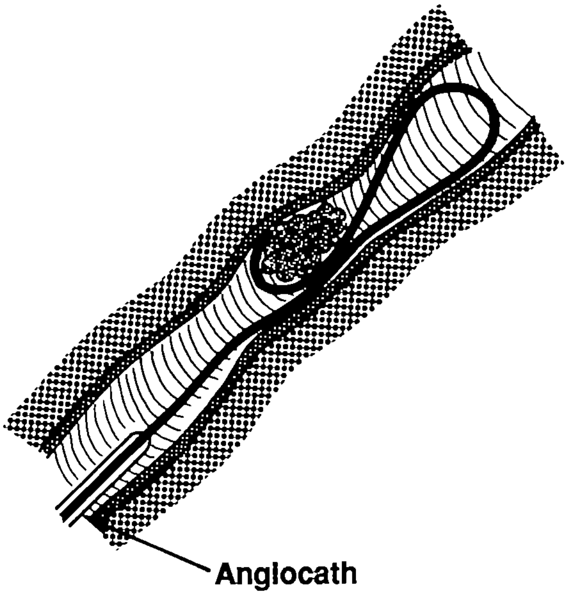

Fig. Diagram of retrograde manipulation using a J-wire.

throughout using an image intensifier C-arm and all patients received a prophylactic intravenous cephalosporin at induction of anaesthesia.

When the calculus was dislodged, either the angiocath or a softer ureteric catheter was taped to a bladder catheter and kept in place until adequate fragmentation had been performed. When attempts at retrograde manipulation were unsuccessful, we usually proceeded directly to percutaneous rigid antegrade ureteroscopy under the same anaesthetic.

Results

A total of 27 patients (49%) underwent successful retrograde stone manipulation using flushing alone. A further 17 (31%) required the additional use of a J-wire for success. Attempts to dislodge the calculus failed in 11 patients (20%). The stone sizes, measured as the maximum diameter, for the 3 groups are shown in the Table.

Observations during attempts at manipulation confirmed that the tip of the J-wire frequently "hooked" the calculus and propelled it upwards into the renal pelvis. This was usually achieved within 3 or 4 passes of the tip alongside the calculus. If unsuccessful at this stage, more prolonged manipulation was unlikely to be successful.

Table Stone Sizes

	No.	*Stone size (mm)* *Mean (range)*
Flushing successful	27	11 (5–20)
J-wire successful	17	11 (7–17)
Unsuccessful	11	14 (8–21)

Four patients (7%) developed complications. One perforation occurred in a tortuous ureter while attempting to pass a guide wire to the level of the calculus. The patient required a temporary percutaneous nephrostomy followed by antegrade ureteroscopy and stenting. One patient developed post-operative septicaemia, which delayed ESWL for 3 days. A patient with a past history of myocardial infarction and ischaemic heart disease developed a further myocardial infarction within 24 h of successful retrograde manipulation. One elderly patient developed respiratory depression after being given intramuscular opiate analgesia for immediate post-operative pain. This was successfully reversed with naloxone.

Discussion

The optimal method of treating upper ureteric calculi with ESWL remains controversial. Initial experience with the Dornier HM3 lithotriptor gave a success rate for *in situ* treatment of only 60% (Miller *et al.*, 1985). The absence of a fluid interface surrounding the calculus probably accounts for problems encountered with *in situ* fragmentation (Mueller *et al.*, 1986; Crum, 1988). Reduced energy requirements to fragment calculi after retrograde manipulation and the diminished need for secondary procedures led to the suggestion that an attempt should be made to manipulate all upper ureteric calculi prior to ESWL (Lingeman *et al.*, 1987). By adopting this policy these authors could manipulate 85% of calculi back into the kidney using a combination of flushing and balloon dilatation. Neverless, they encountered a 5.1% rate of ureteric perforation.

Chadbourne and Lyon (1988), using a larger diameter angiocath and lignocaine gel, reported a 94% success rate for retrograde manipulation without ureteric perforation and they suggested that most perforations occur when a wire or catheter is deflected off the calculus into the wall of the ureter. Flushing from just below the stone, therefore, avoids this complication..

More recently, several second generation lithotriptor machines have been introduced which permit treatment without anaesthesia or analgesia. This makes a trial of *in situ* treatment more attractive. The Wolf 2300 Piezolith uses ultrasound to localise calculi. In our experience, as stones lie more distal in the ureter they become progressively more difficult to localise. Difficulty is also encountered when the ureter adopts a medial course, as this may result in shadowing from the transverse processes. We have reserved retrograde manipulation for calculi which cannot be localised by ultrasound, for those which fail a trial of *in situ* treatment and for large calculi which have a greater chance of incomplete fragmentation with the production of distal obstruction (Parr *et al*., 1991). This policy means that our patients who require retrograde manipulation have larger calculi than in the earlier reported series and probably also have a higher proportion of impacted calculi. These factors probably account for the lower success rate for retrograde flushing alone in our series.

The use of a J-wire increased the success rate considerably for retrograde manipulation. There were no perforations attributable to the J-wire itself and this is probably because the broader presenting surface of the J-wire is less likely to puncture the ureteric mucosa than the tip of a straight wire or rigid catheter. In summary, we feel that this is a simple and safe technique which has enabled a large proportion of our patients to avoid more invasive surgical options such as antegrade ureteroscopy or ureterolithotomy.

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Thiazide Treatment for Calcium Urolithiasis in Patients with Idiopathic Hypercalciuria

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Summary—In a randomised trial based on a parallel design to determine the prophylactic effect of thiazide on stone formation, 210 calcium urolithiasis patients with idiopathic hypercalciuria were allocated either to treatment with trichlormethiazide (4 mg/day) or no treatment with only close follow-up; 35 patients were excluded for various reasons, including voluntary withdrawal. The background of the remaining 175 patients (82 in the thiazide group and 93 in the control group), including age and sex, was similar for both groups. In patients treated with thiazide there was a statistically significant fall in urinary calcium output. Statistical analyses also demonstrated that the stone formation rate in the thiazide group was significantly less than that in the control group. Adverse clinical reactions probably due to the drug were observed in 9 patients. These findings indicate that trichlormethiazide has a prophylactic effect on calcium urolithiasis in patients with idiopathic hypercalciuria.

Although many causes have been implicated in the formation of calcium stones, hypercalciuria is considered to be an important risk factor (Pak, 1988). Previously termed idiopathic hypercalciuria (Henneman *et al.*, 1958), this condition probably comprises at least 2 separate entities—absorptive hypercalciuria and renal hypercalciuria—depending on whether the excessive renal loss of calcium is a result of primary intestinal hyperabsorption of calcium or an impairment in the renal tubular reabsorption of calcium (Pak *et al.*, 1974). Thiazide has been widely used to prevent recurrent calcium urolithiasis and the mechanism of this reduction is probably mediated by the ability of certain drugs to reduce the output of urinary calcium (Coe, 1977). However, questions remain concerning the effects of thiazide. Churchill and Taylor (1985) drew attention to the need for a prospective clinical trial to provide definitive evidence regarding the efficacy of thiazide in preventing recurrent calcium urolithiasis.

In the present study, the efficacy of trichlormethiazide (Schering-Plough, Kenilworth, USA) in preventing calcium urolithiasis in patients with idiopathic hypercalciuria was evaluated in a randomised study based on a parallel design.

Patients and Methods

This randomised trial of trichlormethiazide versus conservative management without placebo in calcium urolithiasis patients with idiopathic hypercalciuria was carried out at the Department of Urology, Kanazawa University Hospital and 14 affilliated hospitals between 1984 and 1990. The patients were required to be at least 16 years of age, not pregnant, without severe renal dysfunction (<0.177 mmol/L serum creatinine), free of urinary infection, with no evidence of obstruction, and having hypercalciuria without signs of primary hyperparathyroidism. All stones obtained by surgical removal and/or stone passage were analysed with an IR-435 infrared spectrophotometer (Shimadzu Co. Ltd, Kyoto, Japan) and shown to contain calcium components, mainly calcium oxalate. The diagnosis of hypercalciuria was based on the presence of 0.10 mmol (4 mg) or more of calcium/kg body weight in 24-h urine (the mean of 2 or more collections) (Coe *et al.*, 1973; Broadus *et al.*, 1978).

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The patients were randomly allocated to 1 of 2 groups, namely treatment with 4 mg trichlormethiazide once a day (thiazide group) or no specific therapy other than supervision and follow-up (control group). In order to minimise the side effects of thiazide, patients allocated to the thiazide group received a half dose of the drug (2 mg) for the first week. All patients in both groups were given the same dietary and fluid advice. No drugs capable of influencing metabolism were allowed during the study. No subjects received potassium supplementation. Compliance with medication was confirmed by verbal communication.

The patients were examined before the trial as in-patients. A 24-h urine sample was collected at least twice while consuming the normal hospital diet containing approximately 15.0 mmol (600 mg) calcium/day. The following substances were determined by standard methods in urine and serum: calcium (total), magnesium, sodium, chloride, potassium, inorganic phosphate, uric acid and creatinine. In addition, ionised calcium was measured by potentiometric determination (Lindgarde, 1972) and serum parathyroid hormone (PTH) was determined using a C-terminal PTH radioimmunoassay kit (Incstar Co., Stillwater, USA). The classification of hypercalciuria was defined according to the system of Pak *et al.* (1975).

In both groups, intravenous urograms were obtained at the initial assessment and at yearly intervals thereafter. Plain abdominal radiographs were also taken at all 3-monthly follow-up visits.

Patients were evaluated as out-patients every 3 months. The response to treatment was assessed according to a modification of the method of Pak *et al.* (1981). The rate of formation of stones, including those which had been voided spontaneously, was calculated for each patient as the number of newly formed stones per year during the time of observation. The group stone formation rate was then calculated as the number of stones newly formed per patient per year. The remission rate was calculated as a percentage per patient per year by dividing the total number of patients without new stone formation by the cumulative number of years of observation. Since this trial was based on a parallel design and hypercalciuria is an important risk factor, the subjects included patients who were first-time stone formers. Therefore, pre-treatment stone formation rates and remission rates could not be calculated.

Side effects and laboratory abnormalities were carefully monitored.

Differences between the 2 groups were compared for statistical significance by Student's, Welch's or paired *t* test, chi-squared test, Wilcoxon rank-sum test and the Mantel–Haenszel method. The data were expressed as mean ±SD.

Results

Initially, 210 patients (105 in each group) entered the study, but 35 patients were excluded for the following reasons: (1) 20 patients in the thiazide group and 12 in the control group withdrew voluntarily (less then 6 months); (2) the thiazide diuretic was discontinued in 2 subjects because of adverse side effects; (3) 1 patient in the thiazide group was given allopurinol and therefore excluded from the study.

The clinical details of the remaining 175 patients (82 thiazide and 93 control patients) are given in Tables 1 and 2; there were no significant differences between the groups with respect to factors such as age (range 16–77 years in the thiazide group versus 17–75 years in the control group), sex, stone composition, classification of hypercalciuria or laboratory data before treatment.

The mean duration of follow-up was 2.21 years (range 6 months–5.7 years) in the thiazide group and 2.14 years (range 6 months–5.7 years) in the control group, which was not a significant difference. The results concerning stone formation are summarised in Table 3. The stone formation rate in the thiazide group was significantly less than that in the control group ($P<0.05$, Wilcoxon rank-sum test). When the rates were compared separately, in single stone patients or multiple or recurrent stone patients, the mean rate in the latter group was higher than that in the former group: this difference was not significant. The mean remission rate in the thiazide group (91.7%) was higher than that in the control group (85.9%), but the difference was not significant ($0.05<P<0.1$, Mantel–Haenszel method).

The pre-treatment data were compared with those obtained at 1 and 6 months, and 1, 2, 3 and 4 years using the paired *t* test.

Urinary calcium levels (mol/mol creatinine) decreased in the thiazide group, with significant differences observed after 1 month and 1, 3 and 4 years ($P<0.01$), whereas in the control group the urinary calcium level did not alter throughout the study period (Table 4). No significant changes in urinary excretion (mol/mol creatinine) of magnesium, uric acid and inorganic phosphate occurred in either group throughout the treatment period. Glycosuria developed in 1 patient.

Table 1 Clinical Characteristics of Patients Evaluated before Treatment

	Study group		
Characteristics	*Thiazide**	*Control*	*Statistical analysis*
No. of patients	82	93	
Age (years) (mean ± SD)	48.7 ± 12.3	46.9 ± 13.8	NS
Sex (male/female)	45/37	52/41	NS
Single stone/multiple or recurrent stone patients	51/31	52/41	NS
Stone composition			
Calcium oxalate/ calcium oxalate and calcium phosphate	17/65	12/81	NS
Classification of hypercalciuria			
Absorptive	32	37	
Renal	19	23	NS
Unclassified	25	27	
Not determined	6	6	
Operation for stone			
Open	34	29	
Endoscopic	28	41	NS
Not done†	20	23	

* Trichlormethiazide. NS = Not significant. † Stone passage.

Table 2 Laboratory and Clinical Data of Patients Evaluated before Treatment

	Study group		
	Thiazide (n=82)	*Control (n=93)*	*Statistical analysis*
Serum			
Total calcium (mmol/L)	2.25 ± 0.15	2.26 ± 0.16	NS
Ionised calcium (mmol/L)	1.20 ± 0.13	1.21 ± 0.13	NS
Magnesium (mmol/L)	0.86 ± 0.12	0.87 ± 0.12	NS
Sodium (mmol/L)	142.1 ± 2.9	141.2 ± 2.7	NS
Chloride (mmol/L)	104.8 ± 2.9	105.5 ± 3.4	NS
Potassium (mmol/L)	3.96 ± 0.38	4.05 ± 0.40	NS
Phosphate (mmol/L)	1.09 ± 0.21	1.03 ± 0.22	NS
Uric acid (mmol/L)	0.28 ± 0.08	0.27 ± 0.08	NS
Creatinine (mmol/L)	0.084 ± 0.017	0.087 ± 0.021	NS
Parathyroid hormone (nmol/L)	0.040 ± 0.027	0.045 ± 0.029	NS
24-h urine			
Calcium			
(mmol/kg body weight)	0.130 ± 0.026	0.130 ± 0.035	NS
(mol/mol creatinine)	0.697 ± 0.254	0.680 ± 0.240	NS
Magnesium			
(mol/mol creatinine)	0.303 ± 0.135	0.372 ± 0.410	NS
Uric acid			
(mol/mol creatinine)	0.342 ± 0.108	0.339 ± 0.128	NS
Blood pressure			
Systolic (mmHg)	127.0 ± 17.6	123.7 ± 18.6	NS
Diastolic (mmHg)	77.4 ± 12.1	74.6 ± 11.6	NS

NS = Not significant. Each value is the mean ± SD.

Serum calcium levels increased significantly after 1 and 6 months ($P < 0.05$) but were stable thereafter in the thiazide group, whereas no significant changes were observed during the study in the control group. Although serum uric acid concentrations significantly increased throughout the study period in the thiazide group, only 3 patients showed mild hyperuricaemia (0.50–0.51 mmol/L) once. In contrast, there were no significant changes in serum uric acid concentrations in the control group. Serum

Table 3 Effect of Treatment on Stone Formation

	Study group		*Statistical analysis*
	Thiazide (n=82)	*Control (n=93)*	
Duration of follow-up (years)	2.21±1.37	2.14±1.33	NS
Total no. of newly formed stones	24	57	NS
Stone formation rate (no. of stones/ patient/year)	0.13±0.33	0.31±0.61	($P<0.05$)
Single stone patients	0.01±0.03	0.02±0.14	NS
Multiple or recurrent stone patients	0.63±0.47	0.97±0.74	NS
Absorptive hypercalciuria patients	0.14±0.35	0.39±0.73	NS
Renal hypercalciuria patients	0.08±0.15	0.26±0.50	NS
Remission rate (%) (per patient/ year)	91.7	85.9	($0.05<P<0.1$)

NS = Not significant. Each value is the mean ± SD.

Table 4 Mean Urinary Calcium Levels before and during Study Period

	Urinary calcium level (mol/mol creatinine) at.					
Group	*1 month*	*6 months*	*1 year*	*2 years*	*3 years*	*4 years*
Thiazide	n=82 0.567* (0.697)	n=54 0.615 (0.728)	n=50 0.570* (0.748)	n=38 0.627 (0.742)	n=20 0.497* (0.720)	n=11 0.545* (0.700)
Control	n=93 0.641 (0.680)	n=43 0.643 (0.635)	n=30 0.677 (0.627)	n=23 0.776 (0.675)	n=10 0.768 (0.632)	n=5 0.598 (0.660)

Values in parentheses are those before treatment. * $P<0.01$ versus pre-treatment values by paired *t* test.

potassium levels remained statistically unchanged in both groups, although 8 patients in the thiazide group showed transient hypokalaemia (2.8–3.4 mmol/L), as compared with no patients in the control group. No statistically significant changes in the serum levels of magnesium, sodium, chloride, inorganic phosphate or creatinine were observed in either group.

Systolic and diastolic blood pressures demonstrated no significant changes in either group, except for significantly decreased systolic pressure after 6 months in the thiazide group ($P<0.01$).

Adverse reactions probably due to trichlormethiazide were observed in 9 patients: dizziness in 6, weakness in 2 and general malaise in 1. Each patient with dizziness or general malaise was removed from the study. Since the symptoms of the other patients were mild, or appeared after administration for more than 6 months, these patients were not withdrawn.

Discussion

The recent widespread use of extracorporeal shock wave lithotripsy and other innovative procedures has revolutionised the treatment for urolithiasis. However, since urolithiasis recurs in a high proportion of patients after stone removal, the importance of prophylactic medical treatment has not diminished.

There have been numerous studies concerning the prophylactic effect of thiazide on calcium urolithiasis (Yendt, 1970; Coe and Kavalach, 1974; Coe, 1977; Yendt and Cohanim, 1978a; Backman *et al.*, 1979; Brocks *et al.*, 1981; Maschio *et al.*, 1981; Pak *et al.*, 1981; Scholz *et al.*, 1982; Ettinger *et al.*, 1988), most of which report that thiazides are efficacious in this clinical situation. This opinion is mainly based on convincing evidence that thiazides decrease urinary calcium excretion (Yendt and Cohanim, 1978b). However, 2 randomised clinical studies have failed to demonstrate a statistically significant decrease in the recurrence rate of calcium urolithiasis patients given thiazides when compared with those receiving a placebo (Brocks *et al.*, 1981; Scholz *et al.*, 1982). These 2 studies may have been handicapped by small sample sizes or by the inclusion of patients without hypercalciuria. On the other hand, Ettinger *et al.* (1988) showed the effectiveness of thiazide (chlorthalidone) in the prevention of recurrent calcium urolithiasis in a double-blind randomised trial. As stressed by Churchill and Taylor (1985), we considered that further randomised clinical trials were needed to elucidate the effectiveness of thiazides.

Most clinical trials of urolithiasis prophylaxis have used historical controls based on self-controlled designs ("before and after" studies) (Louis *et al.*, 1984). This kind of design is considered to have several disadvantages. For example, it cannot separate treatment effect from time and it often lacks symmetry between observations during treatment and control (baseline) period. The results may be biased if disease is not stable and there is no direct comparison with any other treatment modality. Ettinger *et al.* (1988) showed that placebo or ineffective treatment appeared to reduce the stone formation rate by about 60%. On the other hand, parallel designs (Lavori *et al.*, 1983) are considered most scientifically valid. In the present study we performed a randomised clinical trial based on a parallel design in calcium urolithiasis patients with idiopathic hypercalciuria in order to determine whether trichlormethiazide had a prophylactic effect. This study was prospective and randomised, but unblinded. Although a randomised placebo-controlled trial is ideal, it is beset by various logistical and ethical problems: it is difficult to recruit a sufficient number of patients for the statistical analysis, especially for a long-term trial lasting more than 1 year. Since all patients in both groups were followed up similarly, including the same dietary and fluid advice, except for the administration of trichlormethiazide in the thiazide group, errors attributable to stone clinic effect (Hoskins *et al.*, 1983) and statistical regression to the mean (Spector and Park, 1985) were minimised.

Of the 210 patients entered into the trial, 35 (23 in the thiazide group and 12 in the control group) were excluded. The difference in the number of excluded patients differed significantly between the 2 groups ($P<0.05$, chi-squared test). A major reason for the exclusions was voluntary withdrawals, *i.e.* 20 patients in the thiazide group and 12 patients in the control group failed to attend within less than 6 months after entry. We suspect that the higher withdrawal rate in the thiazide group was partly due to intolerance to trichlormethiazide.

The remaining patients were equally matched in both groups, the duration of follow-up was similar, and the data were analysed statistically. Urinary calcium levels in the thiazide group decreased, with significant differences, and remained stable in the control group. The stone formation rate in the thiazide group was significantly less than that in the control group. Treatment also decreased the recurrence rates not only in patients with multiple or recurrent stones but also in first-time stone formers. These differences were not significant, probably because of small sample sizes. Pak (1988) considered that thiazides were ideal drugs for the correction of a renal calcium leak, and they had the further advantages of avoiding the possible development of secondary hyperparathyroidism and of restoring normal 1,25-$(OH)_2D$ synthesis and intestinal calcium absorption. In the present study the mean stone formation rates, not only in renal hypercalciuria patients but also in absorptive hypercalciuria patients in the thiazide group, were less than those in the control group. These differences were not significant, possibly because of small sample sizes. Although Yendt and Cohanim (1978b) reported that intestinal calcium absorption might decrease during long-term administration of thiazide, the effect of thiazides on absorptive hypercalciuria is controversial. Further studies are needed to provide definitive evidence.

With regard to side effects, 6 patients in the thiazide group developed dizziness. However, since the blood pressures of these patients measured during the treatment period did not decrease markedly, transient hypotension may have been responsible. Weakness in 2 patients may have been related to transient hypokalaemia, since their minimum values were 3.1 and 3.3 mmol/L respectively. One patient who developed general malaise had no abnormal laboratory or clinical data, but the symptom subsided with discontinuation of the drug. Glycosuria in 1 patient was probably related to impaired glucose tolerance induced by thiazide (Lewis *et al.*, 1976).

Trichlormethiazide has been statistically demonstrated to have a prophylactic effect on calcium urolithiasis in patients with idiopathic hypercalciuria. However, the drug should be used only in conjunction with careful monitoring of adverse reactions and abnormal laboratory data.

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Dialysis in Patients with Upper Urinary Tract Transitional Cell Carcinoma

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Summary—In some patients with primary malignant disease of the kidney the only way of achieving a cure may involve radical surgery. If the tumour is bilateral or involves a solitary kidney, renal failure may be unavoidable. The role of dialysis and transplantation in these patients following "curative" cancer surgery is not clear. A review of the literature and experience with 4 patients who ultimately had bilateral nephrectomies for multiple recurrent upper tract urothelial malignancy is reported. These 4 patients remained free of tumour recurrence on dialysis at 5, 8, 12 and 72 months respectively since commencing dialysis, although 2 have died from unrelated causes. It would seem reasonable to offer dialysis followed by subsequent transplantation in this group of patients after a period of 1 to 2 years has elapsed without any evidence of malignant recurrence.

The clinical problem posed by bilateral upper tract transitional cell carcinoma is a difficult one and the role of transplantation following a period of dialysis in this situation is unclear. Transitional cell carcinoma (TCC) is a common malignancy which occurs most frequently in the bladder, only 2 to 4% of cases occurring in the ureter or renal pelvis. Transitional cell carcinoma of the renal pelvis accounts for 5 to 7% of all renal tumours (Campbell, 1973; Nocks *et al.*, 1979). If TCC does occur in one upper tract there is a 2 to 4% chance of a similar tumour developing in the contralateral collecting system. The development of bilateral upper tract TCC is therefore uncommon and can often be managed by local resection or even endoscopically. A small number of patients develop progressive multifocal disease which affects both upper and lower urinary tracts, eventually leading to renal failure. We have recently encountered 4 patients with uncontrolled upper tract and/or bladder disease requiring extensive surgery that has included the removal of both kidneys. These patients were managed successfully on dialysis for periods ranging from 5 to 72 months without any evidence of tumour recurrence. These results have encouraged us to question whether such patients should be considered for transplantation and, if so, what would be the optimum timing.

Case Reports

Case 1. B.H., a 50-year-old man, presented in 1972 with several low grade superficial papillary tumours of the bladder. Recurrences were subsequently kept under control for 16 years, when he developed uncontrollable bleeding from extensive tumour recurrences. Radical cystourethrectomy was performed. He returned 5 months later with tumours in both ureters and renal pelves, causing renal failure. Since conservative surgery was not possible, bilateral nephroureterectomy was carried out and the patient was successfully placed on haemodialysis. He died somewhat unexpectedly of a myocardial infarction in April 1989 but at post mortem examination no evidence of tumour recurrence could be found (8 months after the commencement of dialysis).

Case 2. B.M., a 46-year-old man, had a right nephroureterectomy in 1966 for transitional cell carcinoma. Several months later a left lower-third ureterectomy with a Boari flap was performed for a lower third ureteric tumour. In a further attempt at conservative curative surgery a left lower pole nephrectomy was carried out in 1989 for a large transitional cell carcinoma of the left renal pelvis

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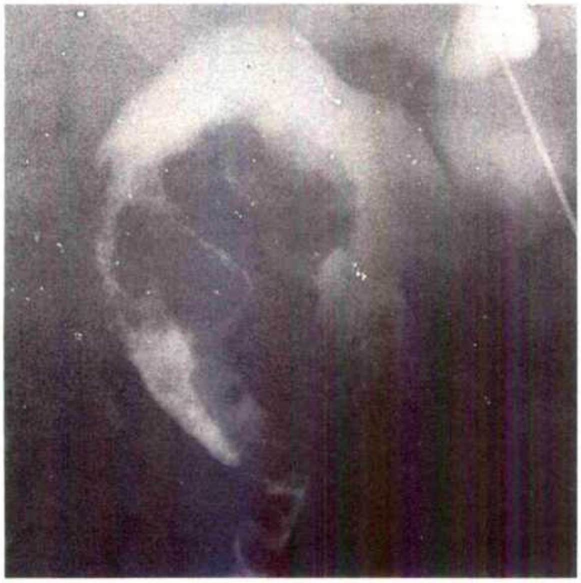

Fig. Antegrade pyelogram of patient with single kidney that had developed obstructive uropathy due to a large transitional cell carcinoma of the renal pelvis.

(Fig.). In December 1989 he developed renal failure due to a further ureteric tumour obstructing the left kidney. Left nephroureterectomy was performed and the patient commenced continuous ambulatory peritoneal dialysis. This patient also died of a myocardial infarction (5 months later) and he too was found to be free of tumour recurrence at post mortem.

Case 3. R.M., a 52-year-old man, had a right lower pole nephrectomy for calculus disease in 1979, followed by a left nephrectomy for staghorn calculi 3 years later. He then developed renal failure as a result of an obstructing high grade invasive transitional cell carcinoma of the ureter. A nephroureterectomy was carried out and dialysis commenced. Although urethrectomy was necessary in 1985 on account of urethral recurrence, and a parathyroidectomy was performed in 1989 for hypercalcaemia, he remains well on dialysis 6 years after his second kidney was removed. Renal transplantation was undertaken 2 years after removal of the second kidney but unfortunately the graft was rejected.

Case 4. D.H., a 37-year-old man, presented with multiple superficial low grade tumours in 1975. These were kept under endoscopic control for 9 years, when total cystectomy was performed as the disease became more aggressive. In 1989 he was found to have invasive tumours in both renal pelves with associated renal failure. Conservative surgery was not possible and bilateral nephrectomies were carried out. He was then put on haemodialysis, on which he has remained without evidence of tumour recurrence for 1 year.

Discussion

Multifocal recurrent transitional cell carcinoma may affect both upper tracts, causing obstruction and, in some cases, leading to renal failure. In 2 of the cases outlined, renal failure developed in a solitary remaining kidney and although conservative manoeuvres were performed, the disease recurred and nephrectomy was eventually necessary, followed by dialysis. In the other 2 cases bilateral nephroureterectomy was performed followed by dialysis. All 4 patients remained free of malignant recurrence at 4, 8, 12 and 72 months respectively, although 2 died subsequently of unrelated causes. These results support the suggestion that, in the small number of patients with multifocal TCC affecting both upper tracts in an unrelenting manner, bilateral nephrectomy followed by dialysis is a reasonable treatment option. If these patients remain free of malignancy for at least 1 year there is evidence to suggest they should then be considered for renal transplantation. The alternative to this is to have repeated attempts at conservative therapy, which may not achieve either of the objectives of preventing renal failure or eradicating the malignancy.

A review of the literature has failed to reveal any experience to suggest how patients who have developed renal failure as a result of upper tract TCC (or as a result of its treatment) should be managed. There have been a few reports concerning the role of dialysis or transplantation in patients following nephrectomy for renal carcinoma. Penn (1977) reported 73 patients who received transplants following nephrectomy for renal carcinoma. Some had undergone bilateral nephrectomy and some had solitary kidneys affected by cancer. He divided them into 2 main groups. The first group comprised patients undergoing antineoplastic therapy within the 12 months prior to transplantation. In this group 53% developed metastatic disease or local recurrence of malignant disease. The second group included patients free of disease for at least 15 months prior to transplantation and in no case did further malignancy develop. It would seem, therefore, that nephrectomy followed by interim dialysis and delayed transplantation is a reasonable approach to patients with cancer in a solitary kidney or to patients with cancer in both kidneys in whom conservative surgery is not feasible. The exact timing of transplantation, however, may be a matter for some debate. Matas (1977) and Penn (1977) suggested that a period of at least 1 year following radical surgery for the tumour should be sufficient. As it seems justifiable to offer dialysis followed by subsequent transplantation to patients with "curable" renal carcinoma, it would also seem appropriate to offer the same treatment to patients with other "potentially curable" malignancies. It has been suggested, for example, that for patients with "good prognosis" cancers, such as low grade skin cancer and carcinoma of the cervix, the presence of malignancy should not preclude the offer of transplantation if it would be otherwise indicated. There have been reports of successful transplantation in patients with either Wilms' tumour in a solitary kidney or with bilateral disease (Belzar, 1972). The criteria for selection of patients for this form of management would seem to be (1) the presence of "curable" malignancy and (2) a significant disease-free period prior to transplantation and no other potentially life-threatening condition. Such patients can be managed on dialysis until they have been free of disease for at least 1 year. Patients in the present series were young and the tumours involved were mainly low grade and potentially curable by radical surgery. The real threat to life was their propensity to cause renal failure in the majority of cases through obstruction of the upper tract.

One consideration if transplantation is offered is whether tumour recurrence is stimulated by the immunosuppression that is used to prevent graft rejection. There is little evidence to support this fear (Doll and Peto, 1987).

Uraemia itself is immunosuppressive and carries with it an increased risk of malignancy. The pattern of malignancy in uraemia, however, differs from that associated with drug-induced immunosuppression. The former comprises a broad spectrum of tumours of visceral and endocrine organs, where the latter consists mainly of skin and lymphoreticular tumours. Matas (1977) treated 10 patients who had developed malignancy while awaiting transplants for renal failure (the aetiology of the renal failure was either glomerulonephritis or polycystic disease). Having removed the malignant primary lesion he then placed the patients on a minimum 1-year dialysis protocol before continuing with transplantation. Although 5 patients subsequently died of unrelated causes, 5 were alive and well (3 at 4 years, 1 at 15 months and 1 at 8 months). Matas's work was encouraging and is not at variance with our limited experience. The groups, however, are not directly comparable, since the tumours in our patients were directly implicated in the renal failure process but were only an incidental finding in Matas's group.

Most clinicians are hesitant or unwilling to consider transplantation in any patient with malignant disease. One of the main reasons for this is the lack of data concerning the results of transplantation in patients with cancer. It is our view that a large-scale review of the results of dialysis and transplantation in patients with malignant disease is required. In particular, the role of transplantation following nephrectomy for renal tumours needs to be defined. If the mortality from the disease is unchanged by offering total nephrectomy and transplantation instead of conservative surgery to preserve renal tissue, then the latter option may be considered preferable in terms of stress caused to the patient and cost-effectiveness. However, in cases where the preservation of renal tissue is impossible or the cancer is not the primary cause of the renal failure (*e.g.* if a potentially curable malignancy exists with coexistent renal failure), there is no doubt that the best option available is dialysis followed by careful consideration for transplantation.

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Long-term Follow-up of Women Treated with Perurethral Teflon Injections for Stress Incontinence

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Summary—The perurethral injection of Teflon has been advocated as a simple, economical and effective treatment of stress incontinence in women. We have reviewed patients treated by this technique in Nottingham. Improvement in their symptoms fell from 80% immediately after operation to 27% at follow-up 3 years later. Because of the disappointing long-term results we have abandoned this procedure for the treatment of stress incontinence.

Stress incontinence occurs when the urethral closure mechanism is incompetent and the urethral closure pressure is less than the pressure within the bladder (Abrams *et al.*, 1988). Surgical correction aims either to restore the normal anatomy of the bladder neck and urethra by elevation, or to increase the urethral resistance (Malvern, 1980; Stamey, 1980). Injection of polytetrafluoroethylene (Teflon) around the urethra has been used as a simple means of curing stress incontinence (Politano *et al.*, 1974).

We have reviewed the long-term outcome of perurethral Teflon injections carried out in Nottingham.

Patients and Methods

A total of 26 women received perurethral Teflon injections for stress incontinence between 1983 and 1986. Their mean age was 63 years (range 27–77). Eleven had undergone previous pelvic surgery (for stress incontinence in 6 cases and hysterectomy for menorrhagia in 5).

All patients underwent synchronous video-urodynamic studies to confirm "genuine stress incontinence" (Abrams *et al.*, 1988). Patients with bladder instability were excluded.

Cystoscopies were performed by senior surgeons and 2 to 3 ml of Teflon were injected at 12, 3, 6 and 9 o'clock to produce bulging of the mucosa and narrowing of the urethra towards the bladder neck. Continence with a full bladder was confirmed at the end of the procedure by abdominal pressure. The mean volume of Teflon injected was 9 ml. Antibiotics and post-operative catheterisation were not routinely used.

Patients were followed up 1 and 3 months post-operatively and discharged if continent. Five patients received a second, and 1 received a third Teflon injection. Some patients returned following failure of their operation at later dates.

All patients were contacted again 3 to 5 years (mean 3.5 years) after the initial operation and further details of continence and side effects were reviewed by consultation.

Results

Patients were assessed subjectively by division into 3 groups:

Excellent: dry, fully continent.

Improved: reduced incontinence.

Unsuccessful: incontinence at pre-operative level.

One month after injection of Teflon, 21 patients (80%) showed improvement, with only 4 (15%) being completely dry. At follow-up 3 years later, only 7 (27%) remained improved, with only 2 (7%) always dry. The rate of recurrence of symptoms is shown in the Figure.

None of the patients receiving a second or third injection of Teflon was continent for more than 6

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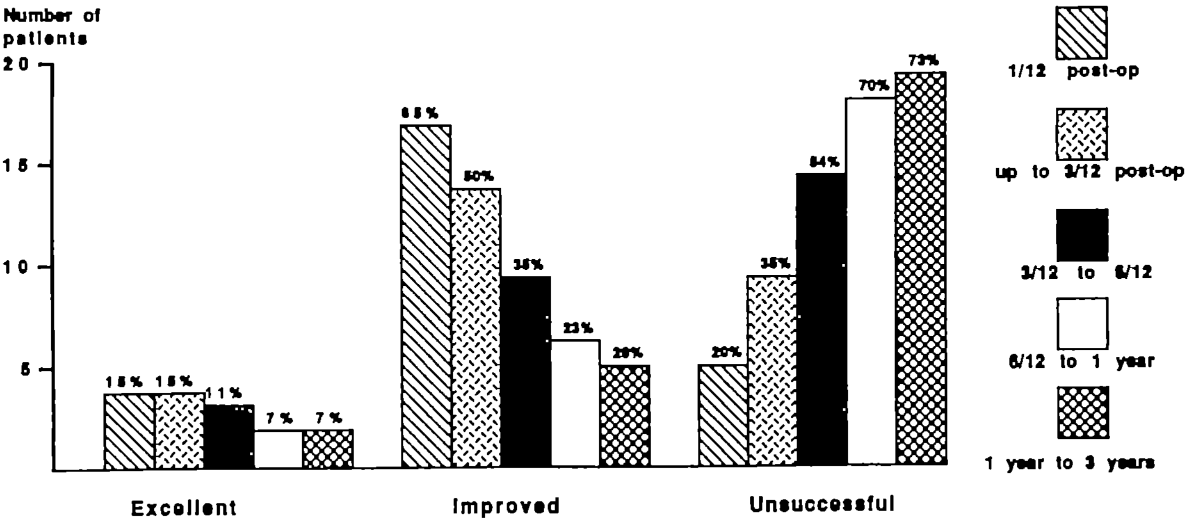

Fig. Duration of improvement in symptoms of incontinence following Teflon injection (n = 26).

months (Table 1). There was no correlation between the total volume of Teflon injected and the success of the procedure.

Complications

Eight patients required catheterisation for 48 to 72 h for retention of urine, and 1 patient was unable to void for 2 weeks (Table 2). There was no correlation between requirement for catheterisation and outcome of the procedure.

Table 1 Overall Outcome with a Minimum 3-year Follow-up

No. of Teflon injections	*Excellent*	*Improved*	*Unsuccessful*	*Total*
1	2	5	19	26
2	0	0	5	5
3	0	0	1	1

Table 2 Complications Following Perurethral Injection of Teflon

Complications	*No. of patients*
Catheterisation	
48–72 h	8
2 weeks	1
Urethral discomfort or dysuria	
<1 week	10
>1 week	4
Passage of Teflon plug	
Painful	2
Painless	1
Urinary tract infections	0

Mild urethral burning and discomfort were common in the first week post-operatively. In 4 cases pain was severe and persisted longer, in 1 case lasting for a month until it resolved with passage of a Teflon plug.

Three patients reported passing Teflon plugs *per urethram* within 3 months of operation. In 2 cases extrusion was accompanied by intense urethral burning pain and loss of continence.

Thirteen of the 19 unsuccessfully treated patients have subsequently undergone further surgery for incontinence (8 received a Stamey colposuspension). All are continent at the present time.

Discussion

Teflon injections for stress incontinence were initially used in patients who had failed to achieve continence with other operations, and in patients with medical problems prohibiting more major procedures (Table 3). Following this the technique has increasingly been used as a first-line treatment of stress incontinence.

Politano *et al.* (1974) first used Teflon for incontinence in men following prostatectomy, and later for women with stress incontinence. They claimed a 56% improvement in this mixed group. The results with male incontinence have been poor in other studies (Deane *et al.*, 1985). In a later series, Politano (1982) showed improvement in 75% of 111 men treated and 71% improvement in 51 women treated. Many patients received more than 1 operation (average 1.8 operations/patient) and follow-up ranged from 6 months to 16 years.

Schulman *et al.* (1984) showed significant im

Table 3 Comparison of Studies Using Teflon Injections for Stress Incontinence

	No. of patients	*Excellent (%)*	*Improved (%)*	*Overall improvement (%)*	*Failure (%)*	*Minimum follow-up (months)*	*Mean volume Teflon paste (ml)*
Politano (1982)	51	51	20	71	29	6	10–15
Lim *et al.* (1983)	28	21	33	54	46	NS	11–20
Schulman *et al.* (1984)	56	70	16	86	14	3	9
Vicente *et al.* (1984)	20	NS	65	65	35	6	9–12
Deane *et al.* (1985)	28	32	29	61	39	3	10
Fischer *et al.* (1986)	20	30	15	45	55	12	6–8
Present study	26	7	20	27	73	36	9

NS = not stated.

provement in 86% of 56 women, of whom 70% were "cured". Deane *et al.* (1985), using similar criteria, achieved a 60% improvement (32% cured). However, in both studies follow-up ranged from 3 to 24 months.

Lim *et al.* (1983) showed improvement in 54% of 28 women treated, but only 21% remained improved at follow-up 1 year later. Exclusion of patients with detrusor instability increased their success rates to 70% (30% cured).

Fischer *et al.* (1986) questioned the place of Teflon injections, having achieved continence in only 30% of patients, with a further 15% demonstrating some improvement. However, 6 of their 20 patients had shown detrusor instability during bladder pressure studies.

The present study compares favourably with these previous reports in terms of patient selection, operative technique, complications and initial outcome, with improvement in 80% (15% excellent, 60% improved). However, in our experience incontinence returned with time in many patients. Furthermore, many of these patients had been discharged from follow-up as successfully treated. A few were referred back by their general practitioners but many had moved from the area, attending other urology or gynaecology clinics, or had given up seeking surgical treatment. These problems may account for the impression of success in other studies.

In 2 patients recurrence of symptoms was directly attributable to the passage of a Teflon plug. It is interesting that 1 patient remained continent for 6 months after passing Teflon urethrally. Furthermore, in a number of patients undergoing repeat cystoscopies, no evidence of Teflon could be seen. Extrusion of Teflon plugs is a well recognised complication, occurring in up to 30% of patients in one series (Vicente and Arano, 1984). Teflon is also known to be absorbed and to "migrate" to deeper sites (Malizia *et al.*, 1984), although no embolic complications have been reported in humans. It is probable that failure of continence is due to a combination of extrusion, absorption and migration of Teflon away from its periurethral site, allowing laxity to return to the tissues and a recurrence of former symptoms.

Among the advantages ascribed to perurethral Teflon injections are the short hospital stay required and the low cost of the procedure. In this study the mean hospital stay was 3 days (range 1–13). Several authors have improved their success rates by repeated injections of Teflon, in some cases up to 4 operations. We found no improvement in the 5 patients injected on more than 1 occasion. With the development of newer procedures with higher success rates and short hospital stays, such as the Stamey bladder neck suspension, we have abandoned the use of Teflon injections for the treatment of stress incontinence.

Initial optimism regarding perurethral injection of Teflon paste as a quick, economical and effective treatment of stress incontinence in women has proved to be misplaced when long-term results are evaluated. We found that 80% of patients are improved initially after treatment, but only 27% after 3 years. Higher success rates reported by other authors using similar techniques and selection criteria merely reflect too short a period of follow-up and early discharge of patients from clinics.

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Subjective and Objective Effects of Intravaginal Electrical Myostimulation and Biofeedback in Patients with Genuine Stress Urinary Incontinence

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Summary—A group of 36 patients (18 premenopausal and 18 postmenopausal), all suffering from genuine stress urinary incontinence, underwent conservative treatment with 6 sessions of intravaginal electromyostimulation followed by 6 sessions of biofeedback; 89% of patients reported an improvement, 5.5% considered themselves cured and 5.5% reported no change. Intravaginal pressure measured before and after therapy increased by an average of 11 cm H_2O in premenopausal patients and 17 cm H_2O in the postmenopausal group. Intravaginal pressure increased in all patients and, according to maximal urethral closure pressure, this increasing intravaginal pressure was observed even in patients with low pressure urethras. The urodynamic factors studied were functional length, maximum urethral closing pressure and pressure transmission, together with urethral surface at rest and during stress, and residual surface. No significant changes were noted before and after treatment. The excellent subjective results contrast with the absence of improvement in these values.

Urinary incontinence is currently an important public health problem that affects 1 in every 2 women to a varying degree at some time in her life. The incidence among patients aged between 15 and 65 years is estimated to be 8.5%, but may be as high as 45% in certain population groups, with as many as 50% of these incontinent patients suffering from genuine stress urinary incontinence (GSUI) (Wolin, 1969; Thomas *et al.*, 1980; Yarnell *et al.*, 1981). Stress incontinence may be cured by surgery, with the success rate for various procedures ranging from 80 to 95%. However, long-term therapeutic results can be considerably lower; for example, only 44% of patients were dry and complication-free following a colposuspension operation (Galloway *et al.*, 1987). Furthermore, a patient may not wish to undergo a surgical procedure with its accompanying risk.

For these reasons there has recently been great interest in the conservative treatment of GSUI by intravaginal electromyostimulation (EMS) and biofeedback (BF) which, with the insertion of intravaginal cones, now complement the physiotherapist's choice of therapy, previously limited to Kegel perineal exercises.

This prospective study was carried out in 36 volunteers referred to the urodynamic unit for assessment and treatment of GSUI with the aim of determining the subjective and objective effects of combined short-term EMS/BF treatment.

Patients and Methods

The series comprised 18 premenopausal women with an average age of 41.7 ± 8 years (range 28–49) and 18 postmenopausal women with an average age of 59.6 ± 6 years (range 51–71). Their selection was based on a history of GSUI according to Ingelmann-Sündberg (1951). All belonged to Ingelmann-Sündberg groups I and II and were similar in parity.

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Urodynamic investigations were carried out according to the International Continence Society (ICS) standards.

(1) Assessment of post-micturition residual urine.
(2) Transurethral abdomino-cystometry carried out by progressive filling of the bladder with 37°, 0.9% saline. The filling rate was 40 ml/min with the patient in the lithotomy position. Maximum bladder capacity was 380 ± 110 ml for premenopausal and 460 ± 113 ml for postmenopausal patients. No patient had detrusor instability.
(3) Recording of the urethral pressure profile at rest and during coughing and calculation of the following urodynamic values: urethral functional length (FL), maximum urethral closing pressure (MUCP), pressure transmission ratio (PTR), urethral surface at rest (USR), urethral surface during stress (USS) and residual surface (RS) (Fig. 1).

The surfaces were calculated with a graphics tablet (model Wiz, CalComp. Inc., Anaheim, USA) and a Macintosh microcomputer.

Urodynamic investigations were carried out with a pneumatic catheter equipped with circular membrane pressure sensors under which air flow remained constant and resistance to flow proportional to the surrounding pressure (Uroset catheter, Metabo Med. Devices, Epalinges, Switzerland). During profile recordings patients were in the semi-recumbent position with 360 to 400 ml of fluid in the bladder. The withdrawal rate of the catheter was 0.25 mm/s.

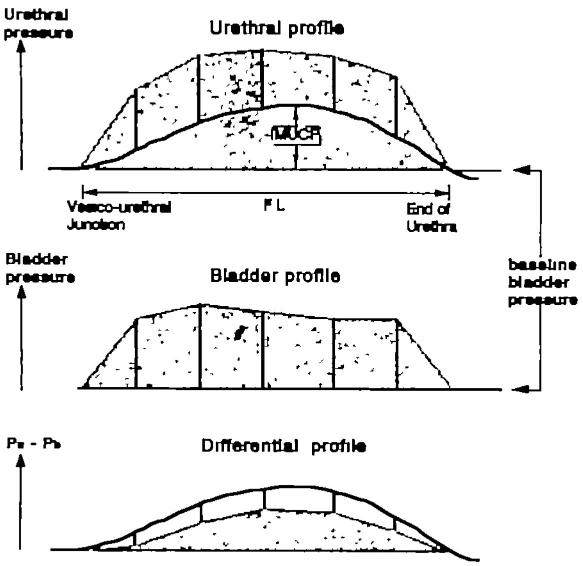

Fig. 1 Graphic representation of urodynamic results. urethral functional length (FL) and maximum urethral closing pressure (MUCP) are indicated. Shaded areas from top to bottom are· urethral surface during stress, bladder surface and residual surface The urethral surface at rest (not shown) is the area under the urethral profile at rest.

Clinical examination was carried out following recording of the urethral stress profile and after removal of the urethrovesical and rectal catheters. Patients were examined with a full bladder and were asked to bear down and cough, initially in the semi-recumbent position and then standing. The presence of urine (either drops or flow) was noted. All patients had clinically demonstrable urinary stress incontinence.

Patients were then referred to the urogynaecological physiotherapy unit, where they underwent 6 sessions of intravaginal EMS with a double surface electrode mounted on a diabolo, placed in the vagina and connected to the neuromuscular stimulator "Compex". The stimulating current was 2-phase, 50 Hz, rectangular current with an impulse length of 22 µs. Contractions lasted 6 s with an interval of 12 s between contractions. The current varied between 25 and 70 mA. The entire EMS session lasted 20 min and there were 2 sessions per week. Patients also underwent 6 sessions of BF carried out with a Kegel perineometer connected to "Physiostim Bio FB2" with a monitor displaying the intravaginal pressure generated by the patient allowing control of her efforts. Sessions lasted less than 30 min, with 2 to 3 sessions per week. Patients were evaluated according to subjective improvement and/or cure of GSUI, protective pad count, daily episodes of urine loss, total daily micturitions and measurement of intravaginal pressure.

After completing treatment the patients performed no further exercises at home and returned for a second examination in the urodynamic unit, where the same values were again measured. Follow-up varied from 6 to 16 weeks between the end of EMS/BF sessions and the second urodynamic evaluation. A 1-tail, paired Student's *t* test was used to compare the values (with standard deviations) obtained for the different groups and categories of patients. A *P* value ≤ 0.05 was considered statistically significant.

Results

Interview

When questioned at the second urodynamic examination, 1 of the 18 premenopausal patients considered herself cured, 15 reported improvement and 2 reported no change in their GSUI.

Of the 18 postmenopausal patients, 1 said she was cured and 17 reported improvement (Fig. 2).

Use of protective pads. Fourteen patients in the premenopausal group did not use protective pads and 4 reported no change in the number of pads employed; 16 premenopausal patients no longer used protection and 2 reported no change.

Daily frequency of micturition. This ranged from 8 ± 4 to 6.7 ± 2 ($P < 0.03$) for premenopausal patients and from 6.3 ± 2 to 5.4 ± 1.3 ($P < 0.01$) for postmenopausal patients.

Biofeedback

Intravaginal pressure before and after 6 sessions of EMS and 6 sessions of BF increased markedly in both groups of patients. Premenopausal patients had intravaginal pressures of 27 ± 18 cm H_2O before treatment and 38 ± 21 cm H_2O after treatment ($P < 0.0001$). Postmenopausal patients had intravaginal pressures of 37 ± 19 cm H_2O before treatment and 54 ± 20 cm H_2O after treatment ($P < 0.006$) (Fig. 3).

Intravaginal pressure before and after 6 sessions of EMS and 6 sessions of BF was also assessed according to the patient's MUCP. In patients with low-pressure urethras (MUCP < 35 cm H_2O) the intravaginal pressure increased from 33 ± 11 to 54 ± 20 cm H_2O ($P < 0.009$). In patients with a MUCP of 35 to 70 cm H_2O the intravaginal pressure increased from 33 ± 23 to 48 ± 24 cm H_2O ($P < 0.0001$). In patients with a MUCP > 70 cm H_2O the intravaginal pressure increased from 25 ± 6 cm to 42 ± 17 cm H_2O ($P < 0.03$) (Fig. 4).

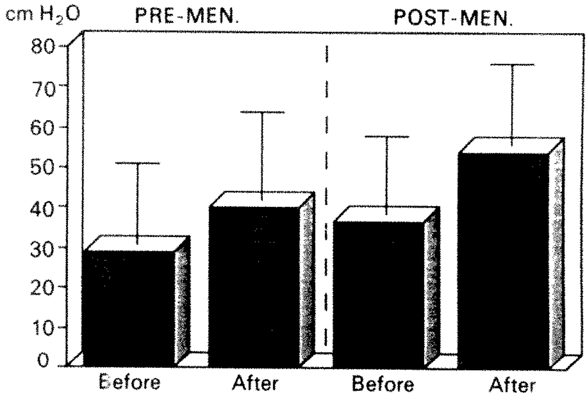

Fig. 3 Intravaginal pressure before and after EMS/BF treatment in premenopausal and postmenopausal patients.

Urodynamic investigations

The urethral stress pressure profiles before and after 6 sessions of EMS and 6 sessions of BF are summarised in Tables 1 and 2. No significant changes were found.

Discussion

The treatment of some GSUI by EMS and/or biofeedback is currently considered a valid alternative to surgical intervention. According to some reports, surgery could be avoided in 53 to 70% of cases (Sheperd *et al.*, 1982; Tapp *et al.*, 1987; Eriksen *et al.*, 1989).

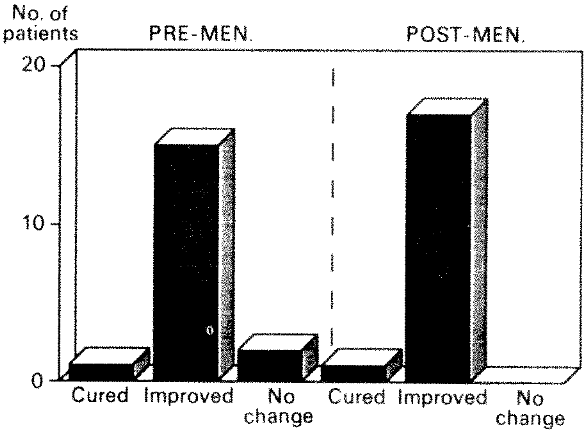

Fig. 2 Data from interviews with premenopausal and postmenopausal patients following 6 sessions of electromyostimulation and biofeedback.

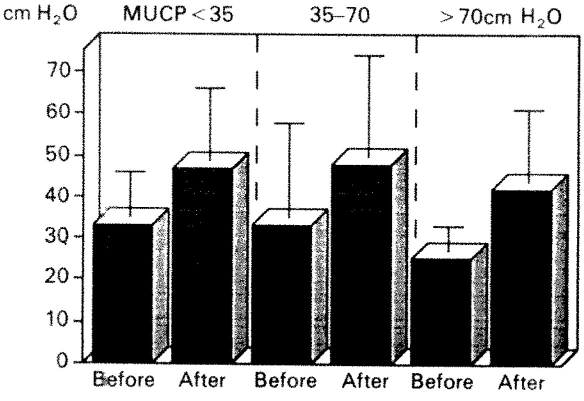

Fig. 4 Intravaginal pressure before and after EMS/BF treatment in patients grouped according to their maximum urethral closing pressure (MUCP).

Table 1 Urodynamic Values: Urethral Functional Length (FL), Maximum Urethral Closing Pressure (MUCP) and Pressure Transmission Ratio (PTR) before and after Electromyostimulation and Biofeedback Treatment

	Premenopausal group (n = 18)			*Postmenopausal group (n = 18)*		
	Before	*After*	*P*	*Before*	*After*	*P*
FL (mm)	26±7	30±6	0 1	30±5	30±7	0.6
MUCP (cm H_2O)	64±23	68±25	0.18	39±11	41±12	0.3
PTR (%)	95±21	100±91	0.3	86±21	93±12	0.2

In the present series of 36 premenopausal and postmenopausal patients with GSUI, 89% were improved and 5.5% were cured. These results are similar to those reported in the literature. Bridges *et al.* (1988) claimed a 90% improvement and a 10% failure rate with interferential therapy. Sheperd *et al.* (1982) found that after BF, 41% of patients were cured and 37% failed to improve. Bent *et al.* (1989) reported a cure rate of 9% and subjective improvement in 87% of patients treated with transvaginal EMS. After 3 months' daily treatment with transvaginal or transanal EMS, Eriksen and Eik-Nes (1989) reported that 68% of patients were continent or improved at the end of treatment, but the percentage was reduced to 56% after 2 years. However, a highly motivated sub-group of 45 patients did have a long-term success rate of 72%. Fall *et al.* (1986) reported improvement in 70% of patients with GSUI and 80% of patients with mixed incontinence, with a long-term success rate of 40% (Fall, 1984). Eriksen *et al.* (1987), in an earlier study on the effectiveness of anal electromyostimulation over a long period of time (average 9 months), found 50% of patients with GSUI cured and 29% improved.

We found that when patients were questioned after this short-term treatment (5–6 weeks) of EMS followed by BF, our results were similar to those of EMS or BF when employed over longer periods.

Values for intravaginal pressure obtained before and after EMS/BF increased by an average of 12 cm H_2O in premenopausal patients and 17 cm H_2O in postmenopausal patients. These values are clearly higher than those obtained by Sheperd *et al.* (1982) who, after BF alone, measured 3.5 cm H_2O in patients with GSUI and 5.5 cm H_2O in continent patients. Dougherty *et al.* (1987) obtained a similar result of 9 cm H_2O, as did Scott and Green (1979) with 13 and 26 cm H_2O. An increase of 11 cm H_2O after BF alone, 4.2 cm H_2O after combined EMS/BF and 15 cm H_2O after combined EMS/interferential therapy was reported by Wilson *et al.* (1987). Others have found that perineometric scoring did not vary (Ramsay and Thou, 1990).

To our knowledge, no previous study has shown a relationship between increased intravaginal pressure and the state of the periurethral environment as reflected by the MUCP. We were surprised to find that when patients were subdivided according to MUCP, a percentage increase in intravaginal pressure was present in all groups (even in patients with low-pressure urethras) and proportional to the MUCP: 60% increase for patients with MUCP <35 cm H_2O, 45% when the MUCP was 35 to 70 cm H_2O, and 68% when the MUCP exceeded 70 cm H_2O.

In this study, the standard urodynamic values (FL, MUCP, PTR) of the urethral stress profile were not significantly modified by EMS/BF treatment. Some reports, however, have shown the opposite. Although significant change in FL and PTR are not mentioned, certain studies have shown

Table 2 Urodynamic Values: Urethral Surface at Rest and during Stress and Residual Surface before and after Electromyostimulation and Biofeedback Treatment

	Premenopausal group (n = 18)			*Postmenopausal group (n = 18)*		
mm²	*Before*	*After*	*P*	*Before*	*After*	*P*
Urethral surface at rest	970±403	1161±507	0.14	820±338	893±417	0.34
Urethral surface during stress	2302±991	2760±1074	0.15	27.48±1019	2627±1052	0.57
Residual surface	763±480	895±632	0.44	352±400	485±507	0.17

a clearly increased MUCP (Bourcier and Juras, 1986; Bo *et al.*, 1990), whereas others reported only a slight increase in MUCP (Eriksen *et al.*, 1987), probably the result of pudendal nerve stimulation rather than direct muscular stimulation (Fall, 1977). Fall *et al.* (1986) concluded that the values of the stress profile remained unmodified. Schüssler *et al.* (1990) reported a 2 cm H_2O increase in MUCP with an improved depression factor in cured patients. No consistent changes in MUCP, FL or PTR following EMS were found by Bent *et al.* (1989) and Wilson *et al.* (1987) reported no significant improvement in MUCP at rest and with stress following BF alone or combined BF/EMS therapy.

Since the MUCP involves only one particular point of the urethral profile, in order to appreciate more precisely the changes over the entire urethral stress profile it is necessary to measure the various surfaces. In this study the USR remained unchanged, whereas Tapp *et al.* (1987) found it to be slightly increased after EMS/BF. The USR and RS were also unchanged.

When EMS alone or BF treatment alone is compared with combined treatment, the therapeutic effect does not seem to change. Tapp *et al.* (1987) found no difference in clinical and urodynamic parameters when patients were treated by BF alone or combined BF/EMS. Wilson *et al.* (1987) also found that the addition of EMS to BF did not significantly improve the treatment of GSUI.

Even though the intermediate and long-term benefits of EMS and BF, observed clinically and by interview, were found to be present in 50% of patients by Sandri *et al.* (1989), this conservative treatment of GSUI produces no significant modification of the urethral profile parameters and surfaces.

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Reconstruction of the Lower Urinary Tract for Neurogenic Bladder: Lessons from the Adolescent Age Group

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Summary—Of 42 adolescents with neurogenic bladder who presented for lower urinary tract reconstruction, 4 patients with severe spina bifida were unfit for major surgery.

Five patients had a simple undiversion; 4 of these had a poor outcome because of unpredicted sphincter incontinence (1 patient) or instability (3).

A total of 26 patients had an enterocystoplasty. All 7 patients who had a substitution cystoplasty had a good result, as did 3 males with a clam cystoplasty. Nine of 16 females had a poor result from a clam procedure. In 3 the problem lay with self-catheterisation difficulties. One each had persistent hyper-reflexia and sphincter incontinence. Four had hyper-reflexia on sexual intercourse.

Overall, 42% of females had problems from the retained bladder segment.

Seven patients had continent urinary diversions. The results were good, although 2 Kock nipples required revision.

Surgery was well tolerated. There was a 21% re-operation rate for complications.

Pre-operative investigation correctly predicted sphincter competence and the need for self-catheterisation in 79 and 86% respectively.

Twenty or more years ago, children who were either born with, or who acquired a neuropathic bladder as a result of spinal disease, could be managed in 1 of 4 ways. Those with upper tract damage, intractable infection or uncontrolled incontinence were usually diverted to a cutaneous stoma. Those who had a suitable bladder and good motivation used manual expression to void. A few were left with a permanent catheter or to dribble into nappies or a sheath.

Now, such children might be taught intermittent clean self-catheterisation (ICSC) or might undergo bladder reconstruction. There is a group of adolescents and adults who are too old to have benefited from these techniques but young enough to wish that they had. This report concerns the management of such individuals. They represent a type of patient who will be seen less often in the future.

Patients with bladder dysfunction due to anorectal agenesis were managed in the same way and are the subject of a separate report, since the bladder problems may not always be due to spinal cord lesions.

Patients and Methods

All patients presenting with neuropathic bladder and unsatisfactory management have been investigated by means of a standard protocol since 1981 (Table 1). On this basis a decision was made on reconstruction. The patients were grouped as follows:

Group 1. Patients with grossly inadequate respiratory reserve, or with internal spinal fixation likely to ulcerate through the skin, were considered inoperable.

Group 2. A stable bladder on cycling with an end filling pressure less than 40 cm of water, a capacity of at least 250 ml and normal ability to void were indications for simple undiversion.

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Table 1 Pre-operative Investigations

Measurement of glomerular filtration rate
Intravenous urography
Examination under anaesthesia
Repeated filling and emptying of the bladder through a suprapubic catheter (cycling)
Videocystometrography after cycling
Teaching and assessment of intermitent clean self-catheterisation

Group 3. A small, unstable bladder that did not empty was an indication for enterocystoplasty providing the patient could self-catheterise.

Surgical technique. The most convenient bowel segments were used. The first choice was the existing ileal conduit, supplemented by another bowel segment if necessary. If the bladder wall was not excessively thick and the unstable detrusor contractions moderate in pressure and frequency, a clam enterocystoplasty was performed (Bramble, 1982). Otherwise, the bladder was excised down to the trigone and a substitution enterocystoplasty performed. The bowel segments were always detubularised. It was assumed that 40 cm of ileum or 20 cm of colon were sufficient completely to replace the bladder. Colon was chosen if the ureters had to be reimplanted into the bowel segment. In females a colposuspension was performed if the leak point pressure was less than 60 cm of water. An artificial urinary sphincter (AUS) was not used unless unexpected sphincter incontinence demanded it as a secondary procedure. One patient had an AUS *in situ* at presentation.

Group 4. Patients who could not self-catheterise the urethra, or whose bladder had been removed, had a continent internal diversion.

Surgical technique. Details of the principles for continent internal diversion have been reported by Cumming *et al.* (1987) and Woodhouse *et al.* (1989). The reservoir was constructed from any remaining bladder or conduit augmented by other intestine if necessary. If bowel was required for the whole reservoir, ileum for a Kock pouch and right colon for a Mitrofanoff procedure were used. Early in the series, the continence mechanism was a Kock nipple, but later the use of the Mitrofanoff principle of a narrow tube (especially the appendix) tunnelled into the reservoir was preferred (Cumming *et al.*, 1987). The catheterisable stoma was sited high on the abdominal wall, just below the xiphisternum if possible, for 5 patients in wheelchairs.

The results have been reviewed up to 1990 and cover the first 10 years. The minimum follow-up was 1 year (mean 3.6).

Results

The study group included 32 females (aged 13 to 44 years) and 10 males (aged 17 to 23 years). The original diagnoses are shown in Table 2; 79% had a congenital spinal cord anomaly. Twenty had a cutaneous diversion and 22 a bladder which had appeared satisfactory in childhood but had become progressively more difficult to control. Eleven patients were in wheelchairs and 2 others had severely impaired mobility.

Group 1 (inoperable): 3 females, 1 male. All of these patients had an ileal conduit with an unsatisfactory stoma either because it was too close to a large skin fold or because it was hidden from the patient by pendulous breasts and abdomen (Fig.). The siting had, according to the parents, been satisfactory in childhood.

Table 2 Diagnoses

Diagnosis	*Female*	*Male*
Spina bifida	20	6
Sacral agenesis	5	—
Spinal neoplasm	3	—
Spinal dysraphism	2	—
Other	2	4
Total	32	10

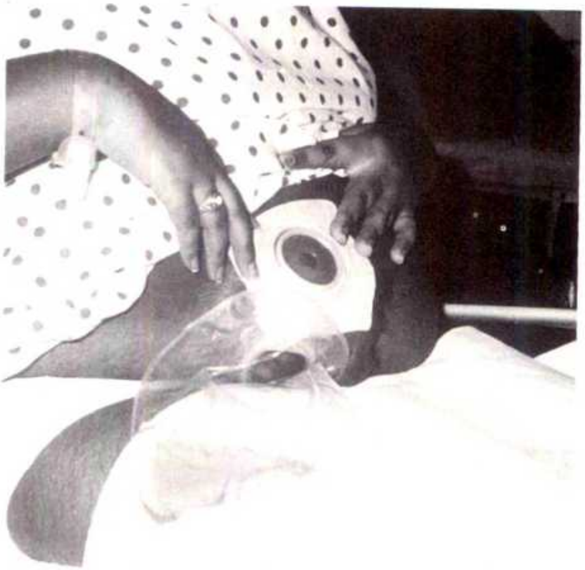

Fig. Clinical photograph to illustrate the difficulty of changing a urinary appliance in a wheelchair when the stoma is too low. The stoma is not in the patient's view.

These patients were considered inoperable for several reasons. The common factors, however, were very poor respiratory reserve, obesity and fixation rods in the spine that threatened to ulcerate.

Group 2 (simple undiversion): 3 females, 2 males. Although preliminary investigation suggested that these patients had bladders that were "safe" for undiversion, the outcome was poor in 4 patients. Two were wet from the outset (1 sphincter incontinence and 1 unstable) and 2 became wet after 3 and 5 years respectively as a result of detrusor instability.

The patient with sphincter incontinence was treated by colposuspension and subsequently by insertion of an artificial sphincter and colocystoplasty, all of which failed to keep her dry. After 2 revisions of the AUS, the cuff ulcerated into the urethra and was removed. She then became dry and now voids by ICSC.

Two of three patients with instability have sufficient residual urine to manage with ICSC (1 having to take oxybutinin as well) and 1 has had a colocystoplasty.

Group 3 (enterocystoplasty): 20 females, 6 males. The distribution of the operations is shown in Table 3. Six of 7 patients with substitution cystoplasty have done well, being continent and emptying by ICSC. One patient has minor incontinence. Another has had a pregnancy which extended to 33 weeks; she then went into premature labour and underwent a caesarean section following failure of cervical dilatation. Both mother and child are well.

Augmentation cystoplasty had a satisfactory outcome in all of 3 males. The results in females were poor in 5 of 16 cases.

In 3 patients the failure was with ICSC rather than the clam itself and they are discussed below.

Table 3 Types of Enterocystoplasty or Continent Internal Diversion

Type	*Female*	*Male*
Augmentation cystoplasty		
Ileum	11	2
Colon	1	1
Mixed	4	—
Substitution cystoplasty		
Colon	3	3
Mixed	1	—
Mitrofanoff	3	2
Kock pouch	2	—
Total	25	8

One patient who had an AUS became incontinent after 4 months when the cuff ulcerated into the urethra. She awaits continent internal diversion.

One patient had persistent incontinence with hyper-reflexia. Excision of the bladder remnant and insertion of an AUS have failed to keep her completely dry.

Four patients exhibited an interesting syndrome that has not been previously described in this situation. All were incontinent with orgasm or, in 1 case, just sexual arousal. All were on ICSC but bladder emptying before intercourse did not solve the problem in 3 as the incontinence was replaced by painful bladder spasms. One had urge incontinence at other times. All were found to have residual detrusor instability. Three have had the residual bladder removed (thus converting to a substitution cystoplasty) and this cured the problem; 1 patient is awaiting residual cystectomy. This problem was not encountered in male patients.

Group 4 (continent internal diversion); 5 females, 2 males. One of 2 Kock pouch patients had a good result. The nipple needed 2 revisions to be continent in the other patient. Three of 5 Mitrofanoff patients had a good result, 2 having stress incontinence which was not severe enough for them to request revision.

Overall surgical results. The patients were young and their tolerance of this major surgery was good. Except for those with very low spinal lesions, it was assumed that the respiratory reserve and ability to expectorate were reduced. All had elective physiotherapy in the early post-operative period. A gastrostomy instead of a nasogastric tube was used for all patients in whom major bowel segments were used. Two patients required ventilation post-operatively.

Re-operations for complications were needed in 21% of patients (Table 4). There were no major early complications related to the abdomen. One patient developed intestinal obstruction 4 months after formation of a Kock pouch. She required prolonged hospitalisation and underwent 2 laparotomies. One patient with severe spina bifida was found dead in bed at home 13 months after the formation of a continent internal diversion; inhalation of vomit was assumed but not proven.

The results of pre-operative investigation showed that 35 patients had a bladder and urethral sphincters which might have been usable. However, in 5 of 7 patients in wheelchairs it became obvious that the urethra was too inaccessible for practical use.

In 29 patients, the pre-operative investigations

Table 4 Complications Requiring Re-operation

Operation	*No. of patients*
Excision of bladder remnant (with AUS in 1)	4
Reversion to ileal conduit	2
Removal of AUS	1
Revision of Kock nipple	1
Colposuspension	
Colocystoplasty + AUS	
Revision of AUS (twice)	
Removal of AUS	1
Total	9

predicted that sphincters would be continent: 23 were dry and 6 (all female) were wet post-operatively. Sphincter incontinence was predicted in 3 patients; this proved correct in 2 but 1 patient was unexpectedly dry. Sphincter continence function was correctly predicted in 79%. Sphincter incontinence was corrected in 3 patients by insertion of an AUS and in 2 by drugs; the sixth patient prefers to remain wet.

In 30 patients the urethra was thought to be the best conduit for emptying the reservoir post-operatively (28 by ICSC and 2 spontaneously). ICSC was learned easily by 25 patients and with difficulty by 3. Post-operatively, 3 patients were able to void spontaneously to completion and 27 practised ICSC, at least initially.

In the long term, 3 of 26 patients discontinued ICSC. One patient had no bladder sensation and was supposed to catheterise by the clock. Unfortunately, she had no concept of time and could not use a clock; she now has a permanent indwelling catheter. Two patients catheterised infrequently and so developed huge bladders and recurrent infections. Both were in end-stage renal failure. When transplantation became necessary they were unable to accept the discipline of regular catheterisation and both reverted to an ileal conduit rather than risk loss of the graft through infection.

Thus pre-operative investigation correctly predicted the post-operative bladder emptying method in 88% of patients.

Examination under anaesthesia was a most useful investigation. The bladder and urethra (if present) were examined. Suprapubic catheters for cycling and urodynamics were inserted. This allowed assessment of access to the abdomen and identification of dangerous areas for pressure sores intra-operatively. It also enabled the anaesthetist to make a practical assessment of anaesthetic tolerance.

Discussion

This was a highly selected group of patients. Their management in childhood was entirely conventional, although not of a type which would be used today. Only about 4% of patients are currently diverted (Brereton *et al.*, 1987). Furthermore, they were sufficiently motivated to accept or even to seek out reconstructive surgery. Adolescents do not always wish to be undiverted: in the author's first series of undiversion patients, 6 of 24 declined reconstructive surgery (Cumming *et al.*, 1988).

The first lesson to emerge from this series is that the lower urinary tract is best treated in childhood. The patients would then have appreciated the more normal social development that occurs without the encumbrance of an external urinary appliance.

It was particularly disappointing to find patients with ileal conduits that were almost impossible to manage and who were unfit for surgery. Adults with spina bifida who are confined to wheelchairs tend to have a fixed curvature of the spine and a very small abdomen. There is often no large flat area, free of skin folds, suitable for application of the bag. Occasionally, the chest may be so protruberant (with or without breasts) that the stoma may be positioned beyond the patient's field of vision.

The 4 inoperable patients all sought reconstruction because of stoma problems of this type. Similar problems were a common motivating factor in the other patients.

The second point concerns the residual bladder, either when used alone or when augmentation is performed. In the present series no problems from the residual bladder arose in the 5 males. In 8 of 19 females (42%) there were problems which required re-operation: persistent hyper-reflexia in 4 and hyper-reflexia unmasked by orgasm in 4.

There is little guidance in the literature on the validity of this observation. It may be due to the selection of patients. Augmentation cystoplasties have not been carried out over a sufficiently long period for there to be a large pool of patients having sexual intercourse. There is a high incidence of sexual ignorance amongst adults with spina bifida. Dorner (1977) found that 23% did not even know how babies were conceived and many more had no knowledge of contraception. None of 8 females with a lesion above L2 were having intercourse, though 1 had orgasm with masturbation; in patients with lower lesions, 17 of 27 had intercourse and 12 experienced orgasm (Cass *et al.*, 1986). Some patients had bladders and there was no mention of any problems with orgasm as a result. A combination of the small number of patients and sexual ignorance may make the syndrome difficult to identify without specific questioning.

It is difficult to select patients with neuropathic bladder and their results from the mass of data in reports on undiversion. Woodhouse (1991) identified about 120 patients reported in the English language literature who had undergone undiversion by clam cystoplasty. Many had not been followed up even for 5 years. There was no suggestion of specific problems from the residual bladder.

Similarly, in 10 children undergoing primary reconstruction by clam cystoplasty for neuropathic bladder, no complications were reported from the residual bladder. All were continent except for 1 with minor "giggle" incontinence (Gearhart *et al.*, 1986).

In patients with detrusor instability undergoing clam cystoplasty, about one-third continue to have unstable contractions post-operatively. These are usually insignificant and do not cause incontinence (Mundy and Stephenson, 1985).

In the present series, 42% of females had problems related to the residual bladder. If it appears that ICSC will be necessary in any event, it would be sensible to do a substitution rather than an augmentation cystoplasty.

The third point is that pre-operative testing can predict sphincter function and the need for ICSC in approximately 75% of patients. It was less accurate at predicting the outcome of simple undiversion. Four of 5 patients had a poor result from simple undiversion despite good early function; it is an unsatisfactory procedure for the neuropathic bladder.

If there is doubt about sphincter continence in females it is advisable to perform a colposuspension at the time of reconstruction.

For the poorest sphincters, an AUS may be indicated. In this series, 2 of 4 AUS cuffs ulcerated into the urethra and had to be removed.

When an AUS is used, ICSC may also be required. If the patient cannot catheterise the urethra, it may be better to provide a suprapubic catheterisable stoma at a more accessible site. This was a contributory indication for all 5 Mitrofanoff procedures.

Finally, the ability of the patient to catheterise should be assessed pre-operatively. Only 2 of 7 patients in wheelchairs learned this technique. The mental attitude to ICSC is obviously important but may be difficult to assess pre-operatively: for example, 2 patients had a satisfactory technique but failed to accept the discipline in the long term.

It is concluded that reconstruction of the neuropathic bladder can be done successfully in adults. Substitution cystoplasty is preferable to augmentation. Patients need careful selection and assessment pre-operatively: 21% of patients require re-operation and half of them need more than one procedure.

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Total Substitution of the Lower Urinary Tract. A Technique for either Reconstruction or Continent Diversion

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Summary—A technique is described in which the right side of the colon is used for substitution cystourethroplasty, based on the flap valve principle, in order to produce a continent catheterisable outflow. The technique can equally well be used for continent diversion.

In 1988 a technique for total substitution of the lower urinary tract in female patients without the use of a prosthesis was described (Mundy, 1988). The substitute bladder was created from the right colon, the substitute urethra from a pedicled labial skin tube and a continence mechanism was produced by a tunnelled anastomosis between them.

The technique remains satisfactory but is technically difficult because the anastomosis between the 2 parts must be performed in the depths of the pelvis, having rotated the labial skin tube up from the perineum and the substitution cystoplasty down from the abdomen.

As a development from the technique of combined substitution cystoplasty and substitution vaginoplasty the current procedure of substitution cystourethroplasty is described. This procedure is easier to perform, is more widely applicable, gives excellent results and can be used interchangeably either for orthotopic substitution cystourethroplasty or for continent diversion.

Patients and Methods

The procedure has been used in 24 patients. Eight female patients had a cystourethrectomy for severe interstitial cystitis which involved the whole of the lower urinary tract, including the urethra, and made simple subtotal cystectomy and substitution cystoplasty inadequate. Four female patients were being undiverted, having previously had the bladder/urethra removed for exstrophy. In these 12 patients the technique was used for reconstruction. Seven patients, 4 female and 3 male, required a total cystourethrectomy for bladder cancer, and 3 female patients had severe lower urinary tract damage following radical radiotherapy and hysterectomy for carcinoma of the cervix. In these 10 patients, and in 2 female patients with spina bifida, the technique was used for continent diversion by placing the catheterisable stoma in the umbilicus, where it was concealed. The 2 spina bifida patients were well motivated adolescents who were considered for orthotopic reconstruction but, because of calipers, were unable to self-catheterise urethrally.

Technique

The right colon is mobilised round to the level of the middle colic vessels—further if the right side of the colon is short for any reason. The gut segment is then mobilised on the ileocolic and marginal artery vascular arcade. The proximal three-quarters will become the bladder and the distal quarter will become the urethra (Fig. 1). The distal quarter of the colon is divided, maintaining continuity of the marginal artery and therefore of the blood supply (Fig. 2). The distal colonic segment is then trimmed so that it can be closed in 2 layers around a 12 F catheter. This forms the neourethra (Fig. 3).

A conveniently sited taenia coli at the distal end

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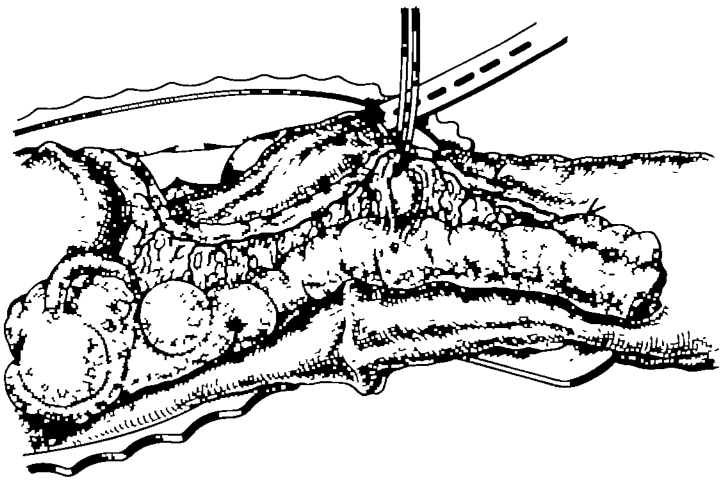

Fig. 1 The right colon round to the level of the middle colic vessels has been mobilised on its vascular pedicle and a window has been made between adjacent vasa recta before dividing the colon to separate the distal one-quarter from the proximal three-quarters, maintaining continuity of the marginal arcade.

of the proposed cystoplasty segment is then incised down to, but not into, the mucosa to create a trench. The mucosa at the tip of this incision is then opened (Fig. 3), and the neourethra is laid into the trench and anastomosed to the hole in the mucosa to create a neourethral orifice (Fig. 4). Tacking sutures are placed to hold the neourethra in the trench, thereby creating a submucosal tunnel and thus a continent flap valve mechanism (Fig. 5). The distal end of the colon is then closed and the ureters are reimplanted by a tunnel technique into the proximal end of the segment. The distal free end of the neourethra can then be either rotated down to the perineum for anastomosis to the perineum if it is intended that the patient be reconstructed, or can be anastomosed to the skin in the depths of the umbilicus if the patient is to have a continent diversion.

Before completing the operation, a careful check is made to ensure that the neourethra is easily catheterisable.

Suprapubic and urethral catheters are left in place until a cystogram on or around the fourteenth post-operative day shows radiological evidence of complete healing. The urethral catheter is removed and the patient started on intermittent self-catheterisation. When this is satisfactory the suprapubic catheter is removed.

Results

All patients are continent on intermittent self-catheterisation. One patient with a continent diversion had stomal stenosis in the depths of a rather deep umbilicus which was revised by

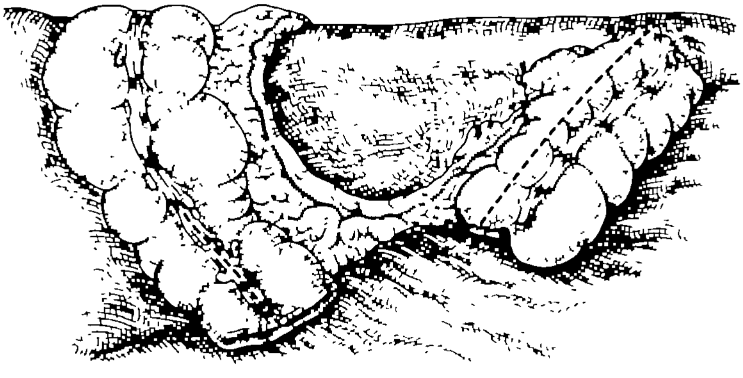

Fig. 2 The future neourethra has been separated from the future substitution cystoplasty. The dotted line shows where the distal segment will be trimmed to size to form the neourethra.

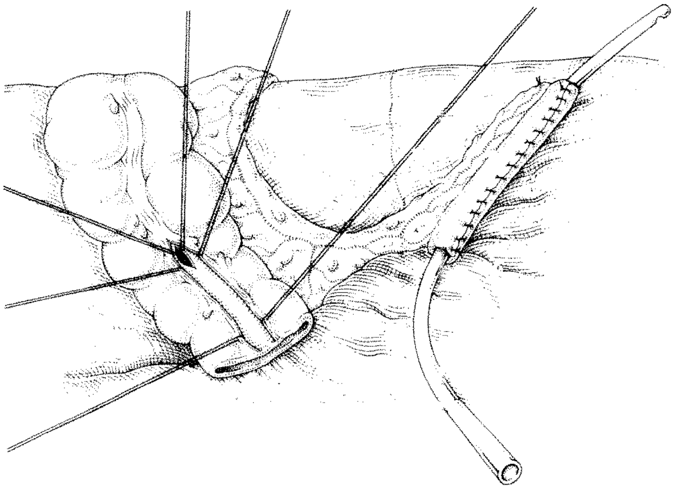

Fig. 3 The neourethra has been constructed and the adjacent taenia coli has been incised to allow the neourethra to be laid in.

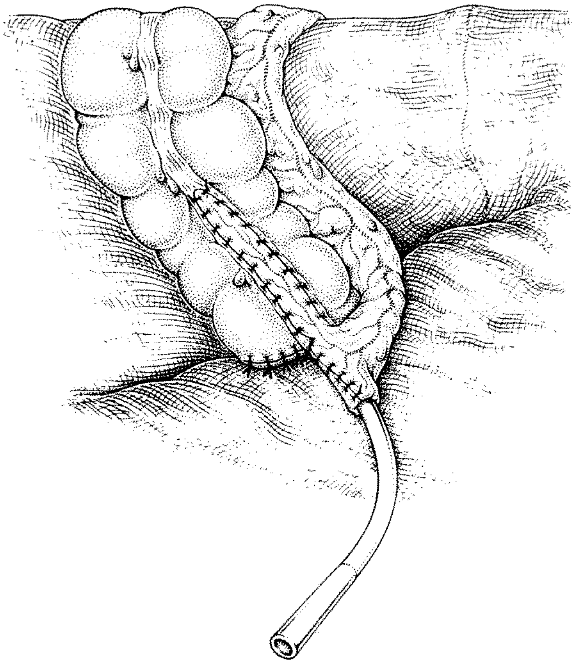

Fig. 4 The completed anastomosis of the neourethra to the cystoplasty.

advancing a "V" flap of umbilical skin. Another patient had difficulty in starting self-catheterisation when the post-operative catheters were first removed, but after a further week of indwelling catheterisation she was able to catheterise without difficulty. One patient had temporary difficulty in self-catheterisation 6 months post-operatively and was treated by indwelling catheterisation; she was able to recommence self-catheterisation a week later.

Discussion

Several techniques have been described that are similar to the present one, principally involving the ileum or the appendix as the catheterisable "neourethra". These operations have the disadvantage that a neourethra is made into the dependent part to the caecum which has a limited range of mobility for exteriorisation of the neo-meatus. Thus, although these procedures can be used for continent diversion, the site of the stoma, and therefore the possibility of reconstructing to a naturally sited meatus may be restricted by the limited range of mobility of the caecum. Ileum is also inherently unsatisfactory because the mucosa lies in circular folds which often make it difficult to catheterise. The alternative of using the appendix may not be possible, either because it is often shrivelled in

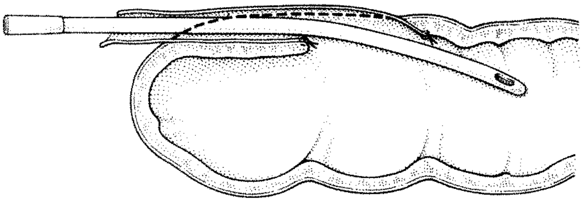

Fig. 5 Diagram to illustrate the flap valve principle to the anastomosis.

adult patients or because it is absent following a previous appendicectomy.

Assuming the right colon is present, the technique described here is universally applicable, and because the neourethra is distally sited in the axis of rotation of the colon around the ileo-colic vessels, it can be used for continent diversion in either sex or for reconstruction in females. The author prefers to reconstruct with a perineal neourethral meatus wherever possible, but 3 groups of patients are more suitably treated by a continent diversion. After pelvic irradiation it is desirable to keep all suture lines out of the pelvis and so continent diversion is indicated for severe irradiation cystitis, post-irradiation fistula and in other similar situations. Secondly, men with transitional cell carcinoma of the bladder who need a urethrectomy as well as a cystoprostatectomy for multi-focal disease, etc, cannot easily be reconstructed because of the problems of creating a full length neourethra. Those with a good prognosis might prefer to have a continent diversion of the type described here rather than an ileal conduit urinary diversion. Finally, there are some patients with spina bifida, similar to those described here, who cannot self-catheterise urethrally because of extraneous limitations such as those imposed by calipers, but who are otherwise suitable for the creation of a continent urinary tract and for whom the only alternative would have been conduit urinary diversion.

Although as yet untried, there is no theoretical reason why the procedure should not also be used for reconstruction in men in whom the urethra is present, but the sphincter mechanism is absent or non-functioning.

Acknowledgement

The figures were drawn by Philip Wilson.

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Open or Transurethral Surgery for the Large Prostate Gland

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Summary—A comparative study of transurethral (TUR) and open prostatectomy for the large prostate gland has been carried out. Over a 5-year period 94 transurethral resections and 73 open procedures were performed for prostate glands weighing more than 50 g. There was a single death in each group, giving relative mortality rates of 1.1% TUR and 1.4% open. The post-operative hospital stay was significantly shorter in the TUR group. The open group suffered significantly more complications in the first week but the TUR patients, although having fewer immediate post-operative complications, had significantly more in the first year, so that overall complication rates were similar (35% *vs* 36%). Patient satisfaction was equal in both groups.

Controversy still exists as to whether an open procedure or TUR is the treatment of choice for the large prostate gland (Lancet, 1989). This debate has been given new impetus following the finding of an increased late mortality rate in patients subjected to transurethral resection compared with open operations (Roos *et al.*, 1989).

The established advantages of short hospital stay and minimal discomfort associated with TUR may now be negated by both high long-term mortality and reoperation rates (Malenka *et al.*, 1990).

We have reviewed short-term to medium-term mortality and morbidity, as well as the patients' perceptions, when comparing TUR with open procedures specifically for the large prostate gland.

Patients and Methods

Over a 5-year period (January 1985–December 1989), 1289 prostatectomies were performed in the Department of Urology at the University Hospital of Wales, Cardiff. The mean weight of resected prostatic tissue was 22 g. Transurethral resection accounted for 94% of cases but only 8% of these had resection weights greater than 50 g (n = 94). The remaining 6% were open procedures (n = 73), with 68 being retropubic prostatectomy and only 5 transvesical. In only 2 patients undergoing open operations were glands less than 50 g removed and these were not included in the study. Preferences within the department of urology meant that one consultant routinely performed retropubic prostatectomy for large glands and the other resected transurethrally. Patients with overtly malignant glands were excluded. Pre-operative assessment of whether glands were large or small was reasonable, with only 13 glands whose resected weights exceeded 50 g being classified as small to medium. Correlation between exact gland size and predicted weight was, however, much worse.

By the time of review all patients had been followed up for a minimum of 1 year. The case records of these patients were reviewed and this was supplemented by a postal questionnaire where applicable. Owing to their age when undergoing these procedures, a number of patients had died by the time of review, often of unrelated pathology.

Of the patients undergoing open operations (n = 73), case records were available for 69 and postal questionnaires were returned by 38 patients. In the TUR group (n = 94), case notes were available in 89 cases and 58 replied to the postal questionnaire.

Five of the patients undergoing transurethral resection had previously undergone TURP (all

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Read at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

benign glands) but none of the open group had undergone previous urological surgery.

All operations were performed by consultant urologists or senior registrars in urology. Statistical analyses were performed using non-parametric tests. The Mann-Whitney U test and the χ^2 test with 95% confidence intervals were used.

Results

Age

There was a statistically significant difference in the mean ages of the patients in the 2 groups, with the older patients tending to have an open procedure (Table 1).

Presentation

Overall, 50% of the operations were performed on patients admitted in acute retention. The majority of open operations were carried out on elective patients (59%) and the majority of TURPs were performed following emergency admission in acute retention (61%).

Operations and hospital stay

The length of post-operative hospital stay and time with a catheter *in situ* was significantly less for patients having a TUR (Table 1). The mean post-operative hospital stay for both groups was more than 7 days. Increasing age of the patient and the development of complications were significant factors in prolonging hospitalisation.

The mean operating times were longer in the TUR group and dependent on the size of the gland resected (Table 2). Significantly more tissue was removed by the open operation than by TUR.

Accurate assessment of blood loss was difficult. The mean drop in haemoglobin was calculated by subtracting post-operative haemoglobin values from the pre-operative value. The mean decrease was greater in the open group than in the TUR patients (2.2 compared with 1.85 g/l) but this was not of statistical significance. There was no difference in the amount of blood transfused to either group, although the mean was slightly higher in the TUR group (0.8 *versus* 1.3 units per patient). Transfusion rates apply only to the immediate post-operative period and do not include secondary haemorrhages. Spinal anaesthesia was given to significantly more patients undergoing transurethral resection to those undergoing an open procedure ($P < 0.05$).

Complications

The complications were divided into 2 groups, those occurring in the first 7 days after operation (early) and those occurring between 7 days and 12 months later (late).

Analysis of complication rates revealed a marked difference in the 2 groups in the first 7 days following operation (Table 3). In the first year (excluding week 1) there were more complications in the TUR group, so that by the end of the first year complication rates were similar. The number and type of complication are shown in Table 4.

Table 1 Details of Patients and Hospital Stay

	Open *Mean (range)*	*TUR* *Mean (range)*	*P*
Age (years)	79 (58–95)	73 (58–90)	<0.01
Weight (g)	92 (50–260)	73 (50–150)	<0.01
Catheter *in situ* (days)	6.4 (3–13)	4.6 (2–14)	<0.001
Hospital stay (days)	9.8 (5–19)	7.1 (3–21)	<0.001
Acute retention (no.)	27 (41%)	54 (61%)	<0.05

Table 2 Details of Operation

	Open *Mean (range)*	*TUR* *Mean (range)*	*P*
Operation time (min)	72 (40–100)	85 (50–170)	<0.01
Resection rates (g/min)	1.3	0.85	<0.05
Spinal anaesthesia	5 (7%)	18 (20%)	<0.05
Blood transfused (units)	0.8 (0–4)	1.3 (0–12)	NS
Drop in haemoglobin (g/l)	2.2	1.85	NS

Table 3 Complication Rates

	Open *No.* (%)	*TUR* *No.* (%)	*P*
Hospital (7 days)	24 (35.5)	16 (17.5)	<0.05
Late (first year)	1 (1.5)	16 (17.5)	<0.05
Overall	25 (36)	32 (35)	NS

Table 4 Complications

Type	*Open*	*TUR*
Early		
Infection (urinary)	10	10
Wound infections	8	0
Chest infections	4	1
Cardiovascular	2*	1*
Primary haemorrhage	0	2
TUR syndrome	0	2
Late		
Secondary haemorrhage	1	8
Stricture	0	4
Reoperation	0	4
Total	25 (36%)	32 (35%)

* includes the single death in each group.

Urinary tract infection was defined as a positive urine culture in patients who were pyrexial but had no evidence of any other source of infection. A red inflamed wound with purulent discharge was classified as a wound infection with 5 of the 8 cases being regarded as minor. Primary haemorrhage was said to have occurred in patients who required further surgical intervention or prolonged blood transfusion for heavy uncontrolled bleeding during the immediate post-operative period.

Secondary haemorrhage was that which occurred following discharge after the first 7 days and was of sufficient severity to warrant hospital admission. Seven of 8 such patients were treated conservatively with irrigating catheters and 6 of the 8 required further blood transfusion. Four patients in the TUR group re-presented with a decreasing flow rate within 6 months: 1 had a submeatal stricture and the other 3 had bulbar strictures. All required further surgical intervention. A further 4 patients presented with acute retention following a failed trial without catheter, for post-TURP retention; in each case a significant amount of benign prostatic tissue was resected, ranging from 13 to 115 g (mean 36) at subsequent operations.

There were 2 post-operative deaths, 1 in each group, both from myocardial infarction in the first week in patients with moderate to severe pre-existing cardiac disease. The relative mortality rates were TUR 1.1% and open operation 1.4%.

Patients' perceptions

Nearly all of the patients who responded to the postal questionnaire were satisfied with their operation and felt their symptoms had improved, despite a high incidence of subsequent sexual dysfunction, particularly retrograde ejaculation (Table 5).

Discussion

With the finding of increased long-term mortality in TUR patients (Roos *et al.*, 1989) the debate on whether to perform an open operation or TUR is continuing with renewed vigour (Neal, 1990). Over the last decade there has been a trend away from open operations towards transurethral resection (Morris *et al.*, 1985). This study has compared the benefits in the short to medium term of these 2 procedures with particular reference to the larger gland. The question of long-term mortality has not been addressed.

The established advantages of TUR compared with open procedures include a shorter hospital stay, minimal discomfort and lower immediate post-operative complication rates (Chilton *et al.*, 1978; Meyhoff *et al.*, 1985), all of which have been confirmed in this study. However, much of this previous work relates primarily to small and medium sized glands with resection weights similar to our overall mean of 22 g.

Reduced physiological strain has been reported with TUR compared with open operations (Meyhoff *et al.*, 1985). This is in part reflected by reduced operating times in the smaller glands. The situation is reversed in the case of large glands, with longer operating times for patients undergoing TUR (particularly those with very large glands). Blood loss is difficult to assess retrospectively but appears similar in the 2 groups. While a smaller drop in

Table 5 Patients' Perceptions

Symptoms	*Open* (%)	*TUR* (%)
Satisfied with operation	89	92
Urinary symptoms: Improved	79	83
Same	21	17
Worse	0	0
Retrograde ejaculation	92	88
Deterioration in sex life (blamed on operation)	46	54

post-operative haemoglobin was noted in the TUR patients this could have been caused in part by the higher intra-operative transfusion rate identified in these patients.

While the mean post-operative hospital stay was shorter in the TUR patients, both groups had long mean stays in excess of 7 days. Pre-operative stays were discounted owing to the large number of patients admitted in acute retention. These patients had a relatively long pre-operation stay while waiting for a place on the next operating list. The age of the patient (Marsh and Whitaker, 1979) and the development of complications (Morris *et al.*, 1985; Wyatt *et al.*, 1989) were important factors in determining the length of hospital stay, rather than the type of operation.

The advantage of low immediate post-operative morbidity seen in the TUR group is lost when complications occurring in the first year are taken into consideration. Pressure of work and the dubious value of following up patients with benign prostatic hypertrophy (Lynch *et al.*, 1991) often mean that the incidence of these delayed complications is not immediately apparent.

Despite prophylactic antibiotics being given to patients with indwelling catheters and/or positive pre-operative urine cultures, urinary tract infection was the commonest complication in both groups. Rates of 15% in open cases and 12% in TUR patients were similar to those in other series (Chilton *et al.*, 1978; Morris *et al.*, 1985; Wyatt *et al.*, 1989), as was the wound infection rate of 12%. The increased incidence of chest infections seen following open operations may in part be explained by the lower number of spinal anaesthetics given to this group together with increased levels of post-operative pain leading to decreased mobility.

Delayed complications occurred almost exclusively in the TUR group. Early stricture rates of 5% (4 of 89 cases) are comparable to those in other studies (Chilton *et al.*, 1978; Mudd *et al.*, 1990). Although the long-term reoperation rates have not been assessed, it is interesting to note that 4 patients needed reoperations within 3 months; presumably this was due to inadequate primary resection of very large glands, since in all cases further large amounts of prostatic tissue were removed. None of the primary haemorrhages was serious but, like the strictures and reoperations, they increased the already heavy demand on hospital beds.

The mortality rates were similar in both groups; they corresponded to those described by Chilton *et al.* (1978) and were confined to high risk cases. It is well established that there is an increased risk to the patient who undergoes prostatectomy for a large gland.

Most patients were satisfied with their operation and reported improvement in their symptoms. Previous clinical studies have shown no statistically significant difference in the outcome of open surgery and TUR (Meyhoff *et al.*, 1984) or indeed in long-term results (Meyhoff and Nordling, 1986). Approximately half of all patients in both groups blamed the operation for a decrease in their sex lives, a finding reported by Malone *et al.* (1988). Whether this dysfunction, excluding retrograde ejaculation, is pathological or psychogenic remains open to debate (Gilbert and Gingell, 1990) but warrants further investigation. All patients questioned about sexual dysfunction were not being followed up regularly and so were unable to complain specifically about sexual problems, but a retrospective questionnaire which enquires about these problems may lead to an overestimated incidence.

In conclusion, the advantages of TUR of large prostate glands (short hospital stay, minimal discomfort and low early morbidity) must be balanced by the higher delayed complication and reoperation rates. It was reassuring to find that patient satisfaction and clinical outcome were equal in both groups. Retropubic prostatectomy still has a place in surgery for benign prostatic hypertrophy.

Acknowledgements

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Laser Ablation of the Prostate in Patients with Benign Prostatic Hypertrophy

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Summary—Seventeen patients with bladder neck obstruction due to benign prostatic hypertrophy have been treated with the Neodymium: YAG laser. We review our experience since the first patient was treated in September 1990.

Using a prototype deflecting gold alloy tip on a quartz laser fibre (Lateralase TM), we ablated obstructing prostatic adenoma and constricting bladder neck tissue. Experience with this technique has enabled a patient population to be defined in whom laser therapy for prostatic obstruction may be effective. The treatment is relatively simple, speedy and attended by virtually no blood loss. Laser ablation therapy may offer some advantages over conventional transurethral resection of the prostate (TURP) in a selected subgroup of patients. The advent of new delivery systems may make laser ablation therapy a practical alternative to TURP.

Although lasers have been used as a surgical therapy since the 1960s, there has not yet been general acceptance of laser photothermal energy in urological surgery. There has been some enthusiasm for Neodymium: YAG laser ablation of papillary transitional cell carcinoma of the bladder, but there does not appear to be a compelling advantage over electrocautery resection for these tumours. No definite improvement in either tumour-free rates or recurrence rates has been found with the Neodymium: YAG laser. There have been reports of its use in benign and malignant prostatic disease, but the inability to deliver laser energy precisely into bulging posterior-urethral adenoma has prevented effective ablation therapy. The lateralase fibre which we used to deflect the laser energy at 90° was originally developed for use in gynaecology to ablate the endometrium. Prior to human trials, laboratory dosimetry and canine experimentation demonstrated a safe and simple technique for ablation (Johnson *et al.*, 1991). There was no evidence of tissue penetration beyond the capsule of the prostate in the canine model at power settings up to 60 W. Although the canine prostate is not exactly a homologue of the human prostate owing to a difference in the stromal epithelial ratios, it is an acceptable experimental model. A pilot study in the human was then undertaken.

The treatment of 17 patients using a lateralase fibre, which has a gold alloy tip attached to the light guide, is summarised. This tip has a deflecting mechanism and photothermal energy is deflected at 90° using a helium neon aiming beam for precise energy delivery.

Patients and Methods

The lateralase^{TM} fibre (Model 20001) (Fig. 1) is a fibreoptic delivery system comprising a 600 μm laser fibre contained in a teflon coated catheter 4 m long. The distal metal tip is glued to the end of a quartz fibre. The metal tip is a 2.5 mm diameter gold plated alloy deflecting dish which allows delivery of laser energy between 40 and 80 watts by reflecting the laser beam at 90°. A helium neon aiming beam is used to control the aiming of Neodymium: YAG laser photothermal energy. The proximal end of the quartz fibre has a standard SMA adaptor. We have used both Surgilase^{TM} and MBB^{TM} Neodymium: YAG generators.

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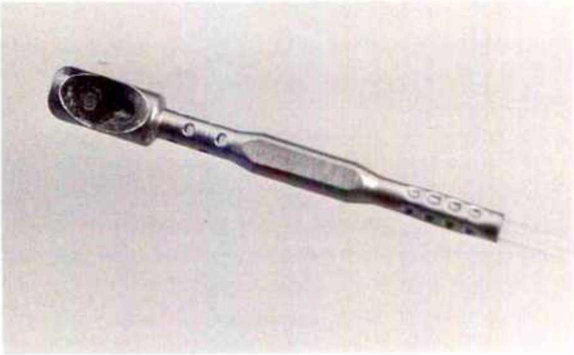

Fig. 1 Tip of the lateralase fibre.

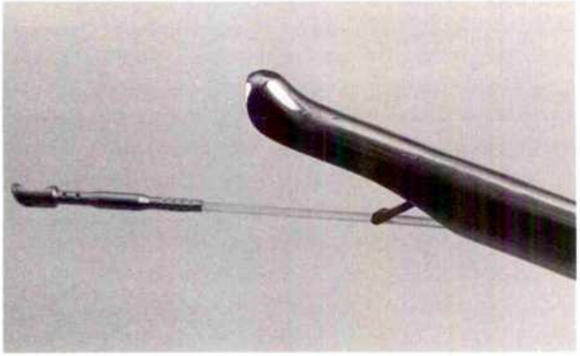

Fig. 2 Laser fibre in the cystoscope.

A standard 23 F cystoscope with a 30° viewing telescope is used and the laser fibre passed through the catheterising port, endoscopically locating the fibre tip in the posterior urethra (Fig. 2).

Seventeen men with a mean age of 69 years (range 60–83) who attended the urology clinic with proven symptoms of bladder neck obstruction were treated. They had palpably benign prostatic enlargement on digital rectal examination. Prior to laser therapy, patients were assessed with a Madsen-Iversen (Madsen and Iversen, 1983) symptom score (Table 1). Investigations included intravenous urography, urinary flow rate, urine culture and routine blood studies, including prostatic specific antigen. Transrectal ultrasound of the prostate was performed immediately before surgery to quantitate prostatic volume and perform ultrasound-guided prostatic needle biopsy. It was necessary to confirm the diagnosis of benign prostatic hyperplasia before commencing laser ablation therapy because no histologically evaluable tissue is extruded for histological analysis during laser ablation therapy.

Cystourethroscopy was performed to evaluate lateral lobe and median lobe prostatic hypertrophy prior to the procedure. All patients were treated under spinal or epidural anaesthesia.

Using standard laser safety precautions, including proper eye protection for operating room personnel and the patient, the fibre was positioned in the posterior urethra, protruding 5 mm beyond the end of the telescope. It was positioned proximal to the verumontanum above the external urethral sphincter. Glycine or water was used for irrigation at flow rates between 100 and 300 ml/min. The laser was set at 60 W power setting on continuous wave. The metal alloy tip of the laser delivery system was placed approximately 1 mm away from the prostatic adenomatous tissue (if brought into contact with the tissue, tip destruction occurs).

Table 1 Symptom Score Questionnaire (Madsen and Iversen, 1983)

Symptom	*0*	*1*	*2*	*3*	*4*
Stream	Normal	Variable		Weak	Dribbling
Voiding	No strain		Abdominal strain or Credé		
Hesitancy	None			Yes	
Intermittency	None			Yes	
Bladder emptying	Do not know or complete	Variable	Incomplete	Single retention	Repeated retention
Incontinence			Yes (including terminal dribbling)		
Urge	None	Mild	Moderate	Severe (incontinence)	
Nocturia	0–1	2	3–4	>4	
Daytime frequency	1 > 3 h	q2–3 h	q1–2 h	q < 1 h	

In an initial pilot study of 4 patients, energy was delivered at 60 W continuous wave for 1 min in 4 quadrants including the roof of the prostatic fossa and floor as well as both lateral lobes (Costello *et al.*, 1992). However, a technical improvement in fibre tip reflectivity after treating these 4 patients led to greater energy delivery in a shorter time, thus reducing lasing in roof and floor areas to approximately 15 to 30 s. For patients with significant median lobe enlargement the laser was used in continuous wave setting at 60 W for approximately 30 s to achieve satisfactory ablation at the bladder neck. Bladder neck ablation is obvious visually and lasing is discontinued when the circular fibres appear. Lateral lobe enlargement is treated by lasing each lobe for approximately 1 min, moving the probe in the posterior urethra as ablation is visualised and the lateral lobes vapourise. During lasing there is often an audible pop or explosion of the adenomatous tissue caused by tissue boiling and vapourisation below the surface of the urethra. An obvious cavity then appears. After vapourising lateral lobe tissue in patients with small volume prostates, the false capsule is exposed, delineating the area of transitional zone hyperplasia.

In patients with prostatic volumes >25 to 30 cc it was difficult to achieve adequate vapourisation and cavitation. In patients with larger prostates (>30 cc) posterior urethral lengths were such that a significant residue of obstructing lateral lobe adenoma did persist. It may be necessary to perform a second lasing after sloughing has occurred over 6 weeks. Intense heat generated at the gold alloy reflector often caused the tip to melt after lasing for 3 to 4 min and if the tip came into contact with prostatic tissue melting occurred more quickly. When the alloy tip melted, lasing became ineffective. It was necessary to remove the fibre tip and clean it if any tissue coated the reflecting surface.

There was no significant bleeding during the lasing procedures. It became obvious that care had to be exercised in positioning the delivery system above the verumontanum and the external urethral sphincter, since inadvertent lasing of the external sphincter could cause significant sphincter destruction and subsequent incontinence. This was not the case in any of our patients.

Patients initially returned to the ward without an indwelling urethral catheter. It became apparent, however, that the burn effect and oedema around the bladder neck caused by lasing at 60 W could cause voiding difficulty and we have reverted to using a 20 F urethral catheter for 48 to 72 h whilst the oedema subsides. A 2-way, non-irrigating 20 F balloon catheter was used. The patients were discharged home the day following surgery and returned to the ward for removal of the catheter at 48 to 72 h. All patients were continent following laser prostatic ablation and none reported loss of erectile potency. The study group included 2 patients in chronic retention with urinary overflow and 1 patient with acute urinary retention. Laser ablation therapy was used in a patient on anticoagulant therapy. Patients were re-evaluated 4 to 6 weeks later with prostatic specific antigen, urinary flow rates, cystoscopy and urinary symptom score.

Results

The results are outlined in Table 2. The mean preoperative symptom score was 15 and the mean preoperative flow rate 5 ml/s. The prostatic volumes, as calculated for an ellipsoid using transrectal ultrasound, were 15 to 35 cc (mean 24). On average, 18 kJ laser energy were delivered per patient with a mean lasing time of 4.2 min. Six weeks after treatment, the mean symptom score fell to 4 (range 1–10) and the mean peak flow rate was 9 ml/s (range 0–21). Two patients with chronic retention and overflow incontinence and 1 patient with acute retention resumed satisfactory voiding patterns following laser therapy. One patient developed retention 3 days post-operatively and this was successfully treated by urethral catheterisation for 24 h. At 6 weeks, 1 patient required a bladder neck incision for persistent bladder outflow obstruction and 2 patients required a TURP. One of these patients had suffered a cerebrovascular accident in the past. Flexible cystourethroscopy under local anaesthesia demonstrated residual occlusive tissue in 7 patients 6 weeks after laser ablation. Ten patients had a prostatic cavity indistinguishable from that seen endoscopically following routine electrocautery TURP.

Discussion

The treatment of benign prostatic hypertrophy is a major health expense for most Western countries. In the USA in 1991, approximately 450,000 transurethral prostatectomies were performed. TURP occupies approximately 25% of the practising urologist's workload. Hospitalisation costs and physicians' charges approximate 5 billion dollars. The economics of this one surgical procedure, first popularised in the 1930s, justify a critical appraisal and audit of its efficacy. Holtgrewe *et al.* (1989)

Table 2 Results of treatment

Bladder outflow obstruction			
Mean pre-operative symptom score (range)	*Mean post-operative symptom score (range)*	*Mean pre-operative flow rate (range)*	*Mean post-operative flow rate (range)*
15	4	5	9
(18–21)	(1–10)	(0–15)	(0–21)
Cystoscopy findings			
Non-occlusive prostatic fossa	Residual bladder neck tissue	Residual lateral lobe	Residual apical tissue
10	2	3	2

reported that 60% of all TUR prostate specimens had a mean weight <20 g. Until recently there has been very little objective audit of the outcome of transurethral resection of the prostate and no critical analysis has been made of post-operative flow rate symptoms. It remains unclear what degree of tissue resection is necessary to achieve adequate improvement in flow rate and a reduction in the symptom score. Marshall (unpublished data) reported, after magnetic resonance imaging studies following transurethral resection of the prostate, that 50 to 60% of prostatic tissue remained *in situ*.

Multi-institutional studies are being carried out on the efficacy of medical therapy for benign prostatic hyperplasia, including alpha blockade, 5 alpha reductase inhibitors and anti-androgen therapy. There is also evaluation of device-related therapies, including balloon dilatation, intra-urethral coils and stents, prostatic hyperthermia and transurethral incision of the prostate.

The ability to resect the prostate with electrocautery remains the hall-mark of a trained urological surgeon and TURP still remains the optimum method for relief of bladder neck obstruction in the majority of patients. Reports from Chute *et al.* (1991) of a slightly higher mortality rate associated with transurethral resection of the prostate when compared with open prostatectomy highlight the necessity for critical evaluation of this surgical procedure.

Although the efficacy of electrocautery resection of the prostate compared with the newer alternative techniques to relieve bladder neck obstruction is beyond doubt, a significant morbidity rate is associated with the procedure. In general, most patients are hospitalised for 4 to 5 days. Regional or general anaesthesia is required and continuous bladder irrigation is often necessary post-operatively to evacuate clot formed in the bladder by bleeding from the prostatic cavity. This bleeding can be quite troublesome and may present a post-operative problem for a small number of patients. Some patients require a blood transfusion following transurethral resection of the prostate. Larger prostates (>50 ml) can occupy lengthy resection times and often require blood transfusion. Lewis *et al.* (1992) reported a 10% transfusion rate in these patients and the potential for transfusion of contaminated blood in the era of HIV infection remains a slight but potential risk. The risk of HIV contamination of the urological surgeon by splash during the resection procedure is also a problem. Urethral instrumentation and post-operative urethral catheters produce an incidence of immediate and delayed urethral stricturing as a sequela of transurethral resection of the prostate in some patients.

Urologists are beginning to apply laser photoradiation for the treatment of prostatic disease. McPhee (1989) employed a Neodymium: YAG laser following TURP to improve haemostasis and noted that all patients had satisfactory post-operative voiding. The technique was cumbersome and there was some difficulty in controlling bleeding from larger vessels at the bladder neck. Beisland and Stranden (1984) used Nd: YAG laser energy 3 to 4 weeks after TURP to treat localised prostate cancer, but found it necessary to insert the flexible laser cable into the prostatic cavity through a suprapubic trocar cystoscope. The procedure was well tolerated, devoid of serious complications and the preliminary results have been encouraging. Similarly, McNicholas (1990) used the Neodymium: YAG laser after an extended TURP to treat early carcinoma of the prostate, causing no immediate alterations in continence or potency.

Shanberg *et al.* (unpublished data) advocated the use of Neodymium: YAG laser to form a prostatotomy for patients with small prostate glands who refused conventional TURP. However, until recently no studies have reported the use of laser energy alone for treatment of prostatic obstruction in the benign gland.

Roth and Areta (1991) studied the transurethral ultrasound-guided laser system to treat the canine prostate for bladder outlet obstructon (Tulip System). This device was developed by the Intra-sonix Company. The procedure combines the Neodymium:YAG laser, a 90° laser microprism, miniaturised transurethral ultrasound imaging transducer for guidance, and a sterile disposal sheath with a 36 F inflatable non-compliant balloon. Treatment resulted in a 3- to 5-fold increase in the diameter of the prostatic urethra and up to 80% reduction in prostatic weight. The equipment is bulky and requires special skill in the interpretation of transurethral ultrasound for laser guidance. Not all urologists are familiar with transurethral ultrasound and this may limit the use of this system. Nevertheless, these studies have proved the feasibility of safe laser prostatectomy. A follow-up report by Assimos *et al.* (1991) confirmed that the Tulip system caused significant tissue ablation in the canine prostate.

Johnson *et al.* (1991) first reported the use of the 600 mm lateralase fibre for transurethral laser prostatectomy in the canine model and described the use of this fibre with conventional urological instruments. This significantly advances the possibility for the urologist to use laser energy to treat prostatic disease, by simplifying laser targeting on the adenoma via a cystoscope.

The lateralase fibre, with its side-firing delivery system, allows delivery of laser photothermal energy precisely into the bulging adenoma. Power density achieved at a power setting of 60 W produces significant ablation and immediate cavity formation, similar to the cavity achieved in electrocautery loop resection. However, the lasing procedure is virtually bloodless and can be accomplished with a lasing time of 3 to 6 min if the volume of the adenoma is less than 30 ml. Not all patients have been found suitable for this type of therapy, but a significant number may benefit from what is potentially a less morbid treatment than conventional electrocautery resection.

There appear to be limitations to the universal use of laser prostatectomy. The cavity formed after ablation can be irregular and ragged. The desiccated infarcted adenoma is not affected by further lasing, the cavity can remain irregular, and the patient passes small amounts of necrotic debris in the urine for 4 to 6 weeks after treatment. However, the urethra is completely re-epithelialised at 6 weeks; this can be confirmed by cystoscopy and at that time the cavity appears more uniform. In a patient not included in this series whose prostate was lased 2 weeks before radical prostatectomy, a 2.5-cm depth of infarction was histologically demonstrated.

When the ultrasound-measured volume of the prostate exceeded 30 ml, insufficient ablation occurred and a repeat procedure some weeks later was sometimes necessary. As yet there is no uniformity of dosimetry and the joules per ml of prostatic tissue required to achieve reproducible ablation are unknown. The lack of fibre durability means that in some procedures more than one fibre was used because of charring and burning of the metal alloy tip. The use of more than one fibre per patient may make this procedure cost-ineffective.

However, the simplicity of this operation, where the uroiogist visually controls the ablation process via conventional urological instruments, seems to make it more attractive than the Tulip ultrasound-guided procedure. The procedure is bloodless and can be completed within 10 min, suggesting that local anaesthesia or a combination of sedoanalgesia and local anaesthesia might be all that is necessary. The patient can be discharged on the same day, with a non-irrigating catheter removed at home at 42 to 72 h. There may be some role for this type of photothermal energy delivery system in prostatic cancer therapy as outlined by McNicholas (1990). Perhaps reduced power settings, a more durable delivery system and real time intra-operative ultrasound will facilitate a more complete tissue removal equivalent to transurethral resection of the prostate. Further evaluation is required.

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P53 and Ki-67 Immunoreactivity in Human Prostate Cancer and Benign Hyperplasia

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Summary—Mutation of the p53 gene is one of the commonest genetic abnormalities found in solid human tumours. This gene is probably concerned with the control of cellular proliferation and in view of this we carried out a study of human prostate cancer and benign prostatic hyperplasia, comparing the expression of mutated p53 with measurement of growth fractions as assessed by staining with Ki-67.

A series of 29 patients with prostate cancer (CaP) were compared with 34 men with benign hyperplasia (BPH); 22 of 29 prostate cancers (76%) contained Ki-67 immunoreactivity compared with 10 of 34 (29%) BPH. With respect to p53 staining, significantly more prostate cancers (17%) were stained than BPH (0%). The mean Ki-67 score in cancers positive for p53 (4.3%) was greater than that found in cancers negative for p53 (1.2%), but no statistically significant relationship was found between tumour grade and Ki-67 staining. The use of Ki-67 and p53 staining may allow identification of tumours with a higher rate of cell growth and may permit development of prognostic factors.

P53 is a 393 amino-acid nucleo-phosphoprotein first identified as a result of binding to the large T antigen of the DNA virus, SV40 (Lane and Crawford, 1979). The p53 gene product inhibits binding of large T antigen to the alpha subunit of DNA polymerase (Gannon and Lane, 1987), but binds strongly to E1B antigen of adenovirus and E6 antigen of polyoma virus. It is a candidate gene for the control of cellular proliferation (Jenkins and Sturzbecker, 1988). The human gene is located on the short arm of chromosome 17 (Miller *et al.*, 1986), which is a common site for allelic deletions in human tumours, often being accompanied by mutations of the remaining allele (Baker *et al.*, 1989; Nigro *et al.*, 1989; Takahashi *et al.*, 1989; Thompson *et al.*, 1990). Transfection studies have shown that the wild type protein is able to suppress cell proliferation and transformation (Finlay *et al.*, 1989; Mercer *et al.*, 1990). However, co-operation has been demonstrated between mutant p53 and mutant ras genes in cellular transformation (Parada *et al.*, 1984; Hinds *et al.*, 1989) and transgenic mice carrying mutant p53 are at increased risk of malignancy (Lavigueur *et al.*, 1989). Initially, these data suggested that p53 may function as a tumour suggressor gene, but it now seems likely that mutations in p53 may also cause it to act as an oncogene under certain circumstances. The p53 protein can undergo self-oligomerisation (Kraiss *et al.*, 1988). It has been proposed that in cells with a single allelic mutation of p53, the mutated p53, which has a significantly increased half-life, oligomerises and inactivates the wild type protein. In addition, the mutated p53 product does not bind to large T antigen and, unlike normal p53 (Braithwaite *et al.*, 1987), does not inhibit SV40 replication. Increased mutations of p53 have recently been reported in several human tumours, including breast (Cattoretti *et al.*, 1988), colon (van den Berg *et al.*, 1989), lung (Iggo *et al.*, 1990) and bladder (Wright *et al.*, 1991).

The monoclonal antibody Ki-67 recognises an unknown antigen present in the nuclei of actively dividing cells (S, G2 and M), but absent in G0.

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Cells in the early stages of transition between G0 and G1, *i.e.* G1T and G1A, lack the Ki-67 antigen, whereas G1 cells after mitosis are Ki-67 positive (Gerdes *et al.*, 1984). The expression of the Ki-67 antigen is an approximation of the numbers of cells which are actively dividing. Previous studies have confirmed that several human tumours express Ki-67 and its role in defining prognosis has been reported in breast cancer (Bouzubar *et al.*, 1989) and non-Hodgkin's lymphoma (Gerdes *et al.*, 1987). Previous studies of prostate cancer have shown that Ki-67 reactivity can be demonstrated (Raymond *et al.*, 1988; Gallee *et al.*, 1989). We have performed the following study comparing immunostaining for p53 and Ki-67 in frozen sections of prostate cancer and benign hyperplasia.

Patients and Methods

A total of 63 men were studied. Of these, 40 (mean age 69 ± 7 years) underwent transurethral prostatectomy (TURP) for bladder outflow obstruction and clinically benign prostate glands; however, 6 of the 40 had areas of unsuspected prostate cancer (T0a and T0b) on subsequent histological examination, leaving 34 with benign prostatic hyperplasia (BPH). The remaining 23 men (mean age 75 ± 7 years; $P < 0.01$ compared with men with BPH) with clinically apparent cancer (T2 = 5; T3 = 12; T4 = 6) (UICC, 1978) underwent TURP for diagnosis or the relief of outflow obstruction. Thus 29 men had prostate cancer and 34 had BPH. Paraffin-embedded sections of each tumour were prepared and grade assessed according to the Gaeta method (Gaeta and Asirwatham, 1983). Because of the predominance of locally advanced disease, most of the tumours were high grade (grade I = 0; grade II = 5; grade III = 15; grade IV = 9). None of the patients with prostate cancer had received previous endocrine treatment.

Fresh prostatic tissue obtained by transurethral resection was placed in ice-cold saline; large undamaged pieces were selected for freezing. The tissue was snap-frozen in isopentane cooled with liquid nitrogen, wrapped in foil and stored in liquid nitrogen. When it came to assessing staining in prostate cancer, only men who had histological evidence of prostate cancer in the frozen material were included in the study and staining was assessed only in the areas of the section occupied by tumour. Specimens with prostate cancer present in the paraffin material, but absent in the frozen material, were excluded.

Antibodies

The following monoclonal antibodies were used. PAb240 recognises an evolutionary conserved epitope on the p53 protein and is highly specific for this protein as demonstrated by immuno-histochemistry, immuno-precipitation and immunoblotting techniques (Gannon *et al.*, 1990). The rat monoclonal Ki-67 antibody was supplied by Dako Ltd (High Wycombe) and has been characterised previously (Gerdes *et al.*, 1984).

Immuno-histochemistry

Serial 5 μ cryostat sections were cut and picked up on lysine coated slides, then air dried for approximately 2 h before fixing in acetone at −10°C for 10 min. The sections were immersed in Tris buffered saline (TBS) for 10 min and incubated in diluted normal rabbit serum (NRS/TBS) for 10 min. A standard indirect immunoperoxidase method was used to demonstrate p53. The sections were incubated with PAb240 as a neat supernatant for 1 h. After washing in 2 changes of TBS they were incubated in peroxidase-conjugated rabbit anti-mouse IgG diluted 1:20 (Dako) in NRS/TBS for 10 min. The sections were washed again in TBS and peroxidase activity developed using hydrogen peroxide–diaminobenzidine solution (Graham and Karnovsky, 1966). For Ki-67, an avidin–biotin technique was used; the sections were incubated in antibody (1:40) for 60 min. After washing in 2 changes of TBS the sections were incubated in biotinylated rabbit anti-mouse immunoglobulin (1:400) for 30 min and then incubated in peroxidase conjugated avidin–biotin complex for 30 min (Dako) as recommended in a concentration of 1 part Avidin, 1 part biotin horse-raddish peroxidase, 125 parts tris-buffered saline (allowed to stand for 30 min before use), followed by washing in TBS. Sites of peroxidase activity were developed using diaminobenzidine diluted in TBS. Sections were counterstained using Carazzi's haematoxylin.

Controls

Positive controls were a squamous carcinoma of the lung (p53) and normal tonsil (Ki-67). Negative controls were included by omitting the primary antibody in each case and replacing it with a non-immune rabbit serum.

Assessment

The staining of all sections was checked independently by 2 pathologists. The proportion of tumour cell nuclei staining was assessed with the aid of a

× 40 objective, a × 10 eyepiece and a 0.09 mm^3 eye piece graticule (E11A, 21 mm, Graticules Ltd). Nuclei in morphologically malignant cells were considered positive for staining when they showed dark brown granular staining; in practice little difficulty was encountered in the assessment of positivity. Random fields in well preserved areas of tumour within the cryostat sections were examined and an average of 2000 malignant cells was counted in each case, the score being expressed as a percentage of cells counted. Whilst some variation between fields was found, the effects of this were diminished by counting these large number of cells.

Statistical analysis was performed by means of tests suitable for data distributed in a non-parametric way. These included the χ^2 test with correction for continuity, the Mann–Whitney test and the Spearman's rank correlation coefficient: a P value of 0.05 was taken as statistically significant on 2-tailed testing.

Results

Ki-67 staining

Of 29 prostate cancers, 22 (76%) were positive for Ki-67 staining, with scores for proportion of cells stained ranging from 0.2 to 9.1% (mean 1.9%). The remaining 7 tumours were not stained. Of 34 cases of BPH, 10 were positively stained (29%; $\chi^2 = 11.6$; $P < 0.01$); the scores ranged from 0.1 to 0.7% (mean 0.19%) and this was a significant difference compared with prostate cancer ($P < 0.001$). There was a suggestion of a weak, but statistically insignificant, relationship between high Ki-67 scores and high grade. For Gaeta grade II tumours the mean Ki-67 score was 0.54% (range 0.2–1.75%); for grade III tumours the score was 1.14% (range 0.2–4.3%) and for grade IV tumours the score was 2.2% (range 0.3–9.1%). The rank correlation coefficient between grade and Ki-67 score was 0.2127 (P not significant).

P53 staining

Of 29 prostate cancers, 5 (17%) exhibited staining for p53, with the proportion of cells stained ranging from 0.2 to 26% (mean 16.7%). The remaining tumours and benign prostates were not stained ($\chi^2 = 4.2$; $P < 0.05$). No statistically significant relationships were observed between p53 staining and tumour stage and grade. However, the mean Ki-67 score in cancers stained positively for p53 (4.3%) was greater than that found in cancers stained negatively for p53 (1.2%; $P < 0.02$).

Discussion

This study has shown that a proportion of prostate cancers contains cells which are stained positively for p53, suggesting that they contain high levels of mutated p53. It has also shown that tumours which are stained positively for p53 are more likely to have a greater Ki-67 score than tumours not stained for p53. It has confirmed previous studies showing that a proportion of prostate cancer cells are positive for Ki-67 (Raymond *et al.*, 1988; Gallee *et al.*, 1989). Mutation of the p53 gene appears to be the commonest mutation yet found in several solid tumours—being identified in about 50% of a variety of human tumours including breast (Cattoretti *et al.*, 1988), colon (van den Berg *et al.*, 1989), lung (Iggo *et al.*, 1990) and bladder cancer (Wright *et al.*, 1991).

Allelic deletions in chromosome 17p have been demonstrated in human tumours, including bladder cancers (Yokota *et al.*, 1987; Mackay *et al.*, 1988; Vogelstein *et al.*, 1988; Tsai *et al.*, 1990) and such deletions are frequently accompanied by mutation of the remaining allele (Baker *et al.*, 1989; Nigro *et al.*, 1989; Takahasi *et al.*, 1989). Iggo *et al.* (1990) found single point mutations in p53 messenger RNA in each of 3 lung cancers showing immunohistochemical evidence of increased p53 protein expression. This evidence is consistent with previous observations that mutation of the p53 protein is usually associated with an increased p53 protein half-life in rodents (Jenkins and Sturzbecher, 1988). A large number of different point mutations have been observed in the p53 gene (Nigro *et al.*, 1989), and the monoclonal antibody PAb240 identifies many, but not all, of these mutations (Bartek *et al.*, 1990; Rodrigues *et al.*, 1990). It is therefore likely that some mutated copies of p53 were not detected by our study. There is good evidence that positive staining with PAb240 is a specific sign of mutated p53, since this antibody binds to a variety of mutants in which there is a common conformational change in the protein (Bartek *et al.*, 1990; Gannon *et al.*, 1990; Rodrigues *et al.*, 1990). However, there is also evidence that certain mutated copies of p53 do not carry an exposed PAb240 epitope (Rodrigues *et al.*, 1990). A recent study from this department has not shown a significant relationship between staining for p53, c-erbB-2 and the epidermal growth factor receptor in human prostate cancer (Mellon *et al.*, 1991).

It seems likely that similar mechanisms underlie our present observations in prostate cancer. Determination of the exact incidence of point mutations of the p53 gene in prostate cancer will probably involve gene sequencing techniques. From recent studies of colo-rectal cancer it is also likely that a further number of the negatively stained tumours will contain mutated p53 protein in which the PAb240 epitope has been exposed (Rodrigues *et al.*, 1990). We found a significant association between staining and Ki-67 staining, suggesting that cells with mutated p53 may be more likely to be actively dividing than those negatively stained for p53. This is in keeping with the putative role of p53 in cell proliferation. A recent study has shown that the p53 gene product and the protein product of the retinoblastoma gene (both genes being tumour suppressor genes) and proliferating cell nuclear antigen (PCNA: an accessory factor to DNA polymerase α) co-localise with infected cell protein 8 (ICP8) in cells infected with herpes simplex virus type I, whereas Ki-67 does not (Wilcock and Lane, 1991). This suggests that Ki-67 is not concerned in the same aspects of cell proliferation as p53 and therefore that one should not necessarily expect a similar pattern of staining in cells positive for mutant p53.

Previous studies of Ki-67 staining in prostate cancer have shown a variable relationship with tumour stage and grade. One study found a significant association between high tumour grade and high Ki-67 staining (Raymond *et al.*, 1988), whereas the other found no such relationship (Gallee *et al.*, 1989). In keeping with previous studies, we found significantly decreased Ki-67 staining in benign hyperplasia. The rate of cell division in prostate cancer is accepted to be lower than in many other solid tumours. For example, in bladder cancer we found a Ki-67 score of 12% in muscle invasive, high grade tumours and about 4% in superficial, low grade tumours (Mellon *et al.*, 1990). Our figure of 1.9% of prostate cancer cells stained with Ki-67 is in keeping with one previous study of prostate cancer using Ki-67 (2.9%) (Gallee *et al.*, 1989) and is also in keeping with studies using *in vivo* labelling with bromodeoxyuridine (BrdU) which showed an overall similar proportion of cells labelled (about 3%) (Nemoto *et al.*, 1989, 1990). On the other hand, a close relationship was reported between BrdU staining and grade and stage of tumour. The figures reported by Raymond *et al.* (1988) of 16.3% of prostate cancer cells stained by Ki-67 are much higher than those of other studies, for reasons that are difficult to explain.

The clinical significance of positive p53 staining in prostate cancer is not yet clear, although it should be noted that most of our tumours were locally advanced and of high grade. It may be that further differences would have been found if T0, T1 or T2 tumours confined to the prostate and suitable for radical prostatectomy had been compared with these high grade, high stage tumours. Further prospective studies are necessary to determine the importance of Ki-67 and p53 immuno-reactivity as a prognostic indicator in prostatic carcinoma. Studies have shown the potential benefit of such markers in bladder cancer with respect to staining for Ki-67 (Mellon *et al.*, 1990) and with respect to staining for the epidermal growth factor receptor (Neal *et al.*, 1990). It may be that prostate cancers demonstrating high levels of p53 staining of Ki-67 staining will behave in a more aggressive fashion than their negatively stained counterparts.

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Phase III Randomised Study of Zoladex versus Stilboestrol in the Treatment of Advanced Prostate Cancer

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Summary—An open randomised Phase III trial was conducted of the depot GnRH analogue goserelin (Zoladex) versus stilboestrol (3 mg/day) in patients with advanced or metastatic prostate cancer. The study included 250 patients and the median follow-up was 43 months. In the Zoladex arm the time to first response was achieved earlier and more patients reported an improvement in symptoms. There was no statistically significant difference between the Zoladex and the stilboestrol arms with regard to survival and time to treatment failure.

A major reason for treatment failure was the preponderance of adverse events in patients receiving stilboestrol. It is suggested that stilboestrol should no longer be used for prostate cancer when equally effective alternative treatments are available.

Following the work of Huggins *et al.* (1941), hormonal manipulation to reduce serum testosterone levels has been the standard treatment for locally advanced and metastatic prostate cancer. Both surgical castration and the administration of oestrogens achieved a good response in patients with advanced prostate cancer.

The large trials reported by the Veterans Administration from the USA showed no survival benefit for oestrogen-treated patients when compared with placebo except in Stage IV patients. When the cause of death of these patients was analysed, however, there was a benefit in cancer-related death but this was outweighed by an excess of cardiovascular-related deaths (Veterans Administration Cooperative Urological Research Group, 1967; Byar, 1973). Many patients find orchiectomy psychologically traumatic.

The search for alternative therapies resulted in the development of analogues of the hypothalamic gonadotrophin releasing hormone (GnRH). This controls the release of serum gonadotrophin (GnH) from the pituitary, which regulates the testicular release of testosterone. Testosterone has a negative feedback effect on both pituitary and hypothalamus. In females, luteinising hormone (LH) and its releasing hormone (LHRH) are chemically identical to GnH and GnRH and the abbreviations are interchangeable.

GnRH analogues have a higher affinity for GnRH receptors than does natural GnRH and their administration causes a surge of GnH from the pituitary, since all of the receptors are bound, with a resultant rise in serum testosterone. The continuing presence of the analogue causes down-regulation of the pituitary receptor and a fall in GnH and testosterone which is sustained as long as the GnRH analogue is present.

Early work showed that the low testosterone level seen with repeated administration of these analogues (Waxman *et al.*, 1983; Perren *et al.*, 1986) was comparable with that seen after orchiectomy. With the introduction of depot preparations of GnRH analogues, which cause a sustained release of active drug, it became practical to use them

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clinically. Clinical reponse rates in Phase II trials showed that a subjective response was achieved in 69% of patients with advanced disease (Beacock *et al.*, 1987), whilst objective responses were seen in 57% of patients (Debruyne *et al.*, 1988) using the analogue goserelin as a depot preparation (Zoladex, ICI Pharmaceuticals). We report the results of a randomised Phase III trial comparing Zoladex with stilboestrol, used at a dose of 3 mg per day, this being the commonly used dose in British urological practice.

Patients and Methods

Patients with prostate cancer, histologically or cytologically proven, with either locally advanced disease (T3 or T4) or metastatic disease were eligible for inclusion in this study. Patients were excluded from entry if they had a history of malignancy within the previous 5 years, radiotherapy to the prostate within the preceding 3 months or prior systemic therapy for prostate cancer. Further criteria for exclusion were patients with contra-indications to oestrogen therapy and those patients with incipient spinal cord compression. In the latter case, the initial rise in testosterone on initiation of therapy with GnRH analogues may exacerbate symptoms from bony metastases—the so-called flare phenomenon—or may lead to spinal cord compression.

Recruitment started in October 1985 and continued until December 1987. The randomisation was stratified by each of the 11 participating West Midlands Urology centres, where local ethical approval had been obtained. Patients were randomised only after fully informed consent. On entry into the trial patients were randomised on a 1:1 basis to receive either Zoladex, a 3.6 mg depot subcutaneously every 28 days, or stilboestrol 3 mg per day orally.

Basic demographic data were collected as regards patients' age, prior history of cardiovascular disease, T category of tumour, pathological grade of tumour, presence and site of metastatic disease, and baseline blood tests including haematology, biochemistry, serum acid phosphatase, alkaline phosphatase and serum testosterone. This allowed comparisons between the 2 treatment groups to be made to ensure there was no bias.

Initially patients were seen at 1 month to check serum testosterone and to assess possible side effects, then at 3 months and 3-monthly intervals thereafter until patients reached a treatment end-point.

Subjective response was assessed by analysing 4 factors: urinary symptoms, performance status, pain from metastases and analgesic requirements for that pain. Each of these factors was given a score from 0 to 4, and a fall of at least 2 points from the same category or a total fall of 4 points was considered a subjective response to treatment. A patient was regarded as symptomatic at entry if he had a score capable of achieving a response, at least 2 in any 1 category or a score of 1 in each of the 4 categories.

Objective response to treatment was assessed by a modification of the British Prostate Group criteria (Table 1) (Chisholm, 1980) and performed 3-monthly. Prostate dimensions were assessed (by digital examination) and serum acid phosphate measured every 3 months whilst an isotope bone scan was performed every 6 months.

The treatment end-point was defined as disease progression, death of the patient or cessation of treatment due to an adverse reaction, or cessation due to the wishes of clinician or patient.

Statistical analysis

Patients' measurements were compared between treatment groups using the Mann–Whitney non-parametric test for continuous measures and Pearson's chi-square test for categorical data.

The time to first response was calculated over the 24 months where patients' response was assessed 3-monthly. Non-responders were censored at 24 months. The log rank chi-square test was used to test for a difference between 2 treatment groups.

The analysis of survival includes all randomised patients in the groups to which they were allocated. Survival was censored at 1 June 1990. Survival curves were drawn using the method of Kaplan and Meier (1958) and the significance of the differences between curves assessed using the log rank chi-square test (Peto *et al.*, 1977).

The time to a treatment end-point was calculated for all patients, as defined above, and censored at 1 June 1990.

Results

A total of 250 patients were randomised, 124 to receive Zoladex and 126 to receive stilboestrol. The entry characteristics (Table 2) demonstrate that the 2 groups were evenly matched with no significant difference between them.

Serum testosterone was measured in 208 patients at entry and after 4 weeks. In 22 of these 208 patients, serum testosterone levels were below

Table 1 Criteria of Response—Definitions Used at Each 3-month Assessment

Category	*Definition*
Complete reponse	No evidence of residual disease
Partial response	*Any of.* Decrease in prostatic size by 50% (product of 2 prostatic dimensions) Decrease in number of lesions or improvement in existing lesions seen on bone scans Decrease in acid phosphatase to at least 80% of pre-treatment value, if initially raised Radiological evidence of healing of any osteolytic bone lesions Decrease in size by 50% of any measurable extraskeletal metastases
Stable disease	Insufficient evidence for response or progression
Progression	*Any of.* Increase in prostatic dimensions by 25% New lesions on bone scan or worsening of existing lesions Appearance of new extraskeletal metastases or increase by 25% of size of existing lesions

Adapted from British Prostate Group criteria (Chisholm, 1980).

Table 2 Comparison of Entry Criteria between Patients Allocated to Each of the 2 Treatment Arms

		Zoladex arm (n=124)	*Stilboestrol arm (n=126)*	*P*
Median age (range) (years)		72.4 (45.6–86.6)	72.6 (52.2–93.1)	0.75
Degree of tumour differentiation No. of patients (%)	Well	21 (17)	23 (18)	
	Moderate	39 (31)	45 (36)	0.85
	Poor	45 (36)	41 (33)	
	Not assessed	19	17	
Patient symptomatic (score >0 see text) No. of patients (%)	Yes	76 (61)	78 (62)	
	NO	46 (37)	47 (37)	0.98
	Not known	2	1	
Known prior cardiovascular disease No. of patients (%)	Yes	35 (28)	35 (28)	
	No	87 (70)	90 (71)	0.90
	Not known	2	1	
Metastatic disease present No. of patients (%)	Yes	92 (74)	85 (67)	
	No	26 (21)	37 (29)	0.14
	Not known	6	4	
Serum acid phosphatase* No. of patients (%)	Normal range	40 (32)	48 (38)	0.35
	Above normal	70 (56)	65 (51)	
Alkaline phosphatase* No. of patients (%)	Normal range	57 (45)	56 (44)	0.90
	Above normal	65 (52)	66 (52)	
Mean serum testosterone (range)	(nmol/l)	12.0 (1.0–31.0)	13.4 (0.6–50.0)	0.49

* Means and median values not used since each hospital had a different normal range, hence non-comparable.

3.5 nmol/l (castration levels) prior to treatment and remained below 3.5 nmol/l after 4 weeks. They had fallen to below 3.5 nmol/l in 89 of 94 patients (95%) on stilboestrol and in 87 of 92 patients (95%) on Zoladex ($P=0.91$).

Subjective response

This was assessed in the 111 patients who had symptoms from their disease at entry (Table 3) as determined by scoring urinary flow, performance status, cancer-related pain and analgesic use for that pain; 46/58 (79%) of the patients in the Zoladex arm achieved an improvement in their symptom score compared with 32/53 (60%) of patients in the stilboestrol arm, a statistically significant difference ($P=0.03$).

Table 3 Symptoms at Entry—Number of Patients with Symptoms as Assessed by Symptom Score

Symptom	*Zoladex arm*	*DES arm*
Urinary flow	22	23
Performance status	15	12
Cancer-related pain	32	34
Analgesic requirement for pain	25	24
*Total number of patients with any of the above symptoms	58	53

*Many patients had symptoms in more than one category

Objective response

The time to first objective response (partial or complete) was measured in 248 patients (Fig. 1), 2 patients having refused their randomised therapy and refusing further follow-up, hence inevaluable for response; 88 patients never achieved a response (Table 4). Of the responders, the median time to first response was 3 months for the Zoladex arm and 6 months for the stilboestrol arm. This was statistically significant ($P=0.035$).

Time to treatment end-point

The time to a treatment end-point for each patient is shown in Figure 2, with the reasons for that end-point shown in Table 5. The median time to a treatment end-point in patients randomised to Zoladex was 15 months, and 11 months in those randomised to stilboestrol.

Survival

Three patients were lost to follow-up and are included in the survival analysis to the date of their last follow-up. After a median follow-up of 43 months (range 9–57) the median survival was 27.5 months (Brookmeyer–Crowley 95% Confidence

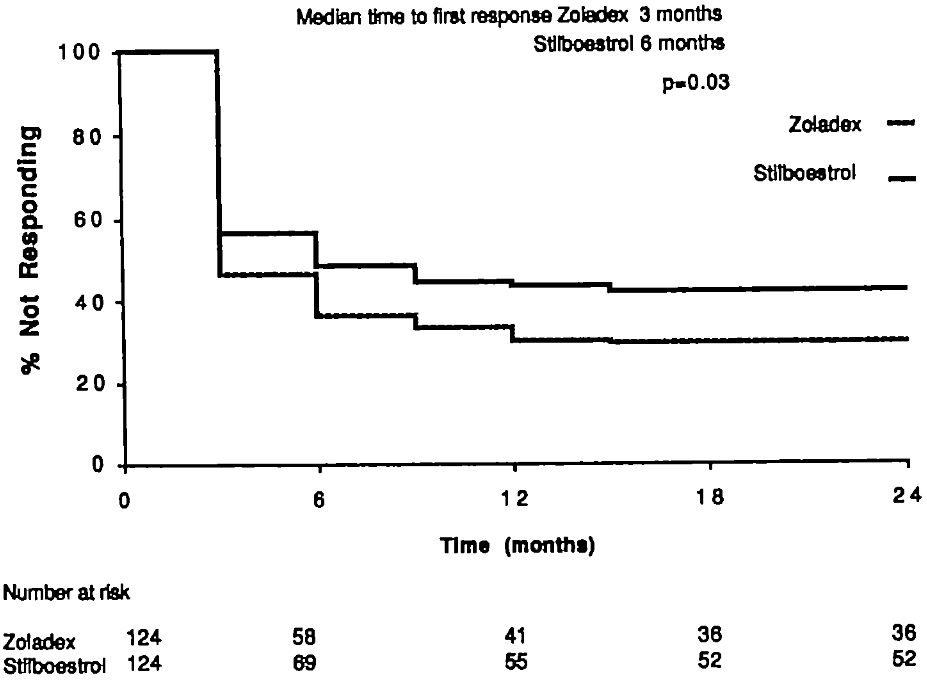


Fig. 1 Time to first response for each treatment group.

Table 4 Objective Response by Treatment—Numbers of Patients Falling into each Response Category at the Time of their Best Response, as Defined by Modified BPG Response Criteria

	Zoladex arm	*Stilboestrol arm*	*Total*
Complete response	9	14	23
Partial response	79	58	137
Non-responders	36	52	88
Total	124	124	248

$P = 0.032$

Intervals 24.2–30.9 months) with no significant difference between the 2 treatment groups (Fig. 3). In those patients treated with Zoladex, 84 died (68%) as compared with 81 deaths (64%) in the stilboestrol group ($P = 0.88$).

Toxicity

The reported adverse events whilst on treatment are listed in Table 6, with the majority of events leading to treatment withdrawal occurring in the stilboestrol group. Of the 54 adverse events in those patients on stilboestrol, 16 were due to a cardiovascular cause. In the Zoladex arm 22 adverse events were reported, being predominantly either transient increases in bone pain—the flare phenomenon (6 patients)—hot flushes (6 patients) or headaches or dizziness (6 patients).

Discussion

Surgical orchiectomy or oestrogen therapy has been the standard method of hormonal manipulation for advanced prostate cancer. A disadvantage of orchiectomy is the need for surgery with its associated morbidity and it may be psychologically unacceptable to patients. Stilboestrol is associated with a high incidence of cardiovascular complications, particularly at a dose of 5 mg per day as used in the initial VACURG studies (Veterans Administration Cooperative Urological Research Group, 1967), but also at lower doses of 1 mg per day (Bailar *et al.*, 1970).

Gonadotrophin releasing hormone analogues achieve a medical castration by blocking gonadotrophin release from the pituitary and thus reducing testicular production of testosterone. This study showed that 95% of patients treated with Zoladex

Table 5 Reasons for Reaching a Treatment End-point

	Zoladex arm	*Stilboestrol arm*	*Total*
Disease progression or death	53	30	83
Adverse reactions	2	36	38
Other	4	7	11
Total	59 (45%)	73 (55%)	132

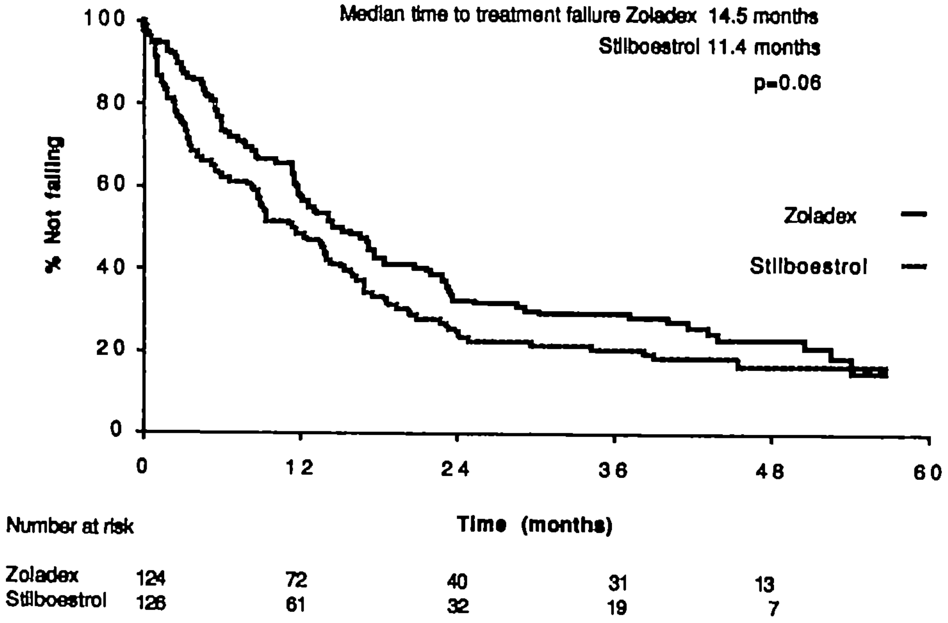
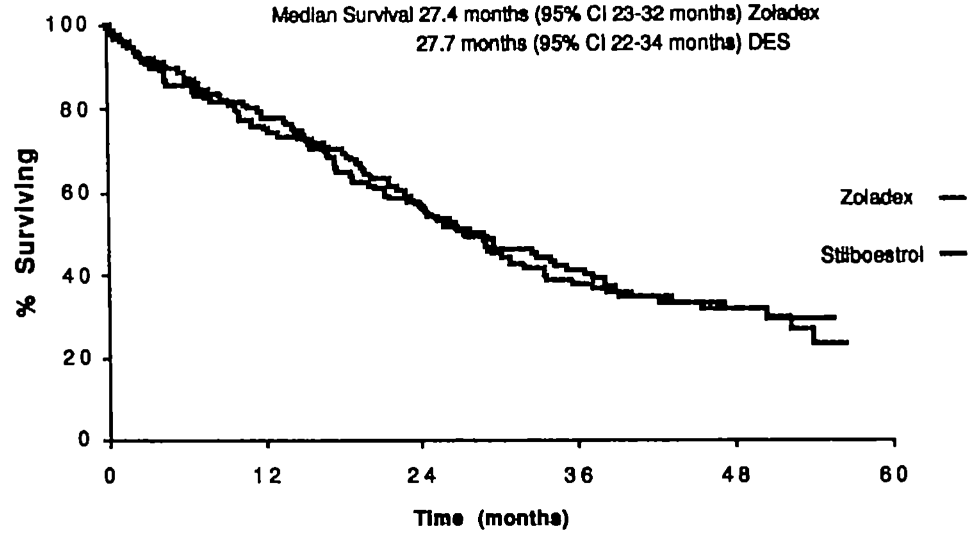


Fig. 2 Time to treatment failure for each treatment group



Number at risk

Zoladex	124	94	70	40	19
Stilboestrol	126	97	69	40	17

Fig. 3 Survival curves for each treatment group.

Table 6 Adverse Reactions—Total Reported Adverse Reactions Showing Number of Events

Event	*Zoladex*	*Stilboestrol*
Angina or myocardial infarction	0	4 (4)
Stroke or transient ischaemic episode	0	6 (4)
Phlebitis or venous thrombosis	0	6 (5)
Pulmonary embolus	0	1 (1)
Severe gynaecomastia	0	12 (5)
Increased bone pain	6 (1)	1 (1)
Spinal cord compression	1 (0)	1 (1)
Nausea and vomiting	1 (0)	8 (6)
Headaches/dizziness	7 (0)	4 (1)
Diplopia/blurred vision	0	2 (2)
Exacerbation of peripheral vascular disease	0	1 (0)
Troublesome hot flushes	6 (0)	4 (2)
Oedema/fluid retention	1 (1)	3 (1)
Leg cramps	0	7 (1)
Skin rashes	1 (0)	3 (0)
Orchitis		1 (1)
Renal impairment	1 (0)	
Increased bruising		1 (0)
Malaise		1 (1)
Total	24 (2)	66 (36)

Figures in parentheses are numbers of events leading directly to withdrawal from therapy.

achieved a fall in serum testosterone to castrate levels within 4 weeks. A similar fall in serum testosterone was seen in the oestrogen-treated patients. When measured in patients undergoing a surgical orchiectomy, testosterone fell in a similar proportion (Robinson and Thomas, 1971; Ryan and Peeling, 1988).

There was no significant difference in survival between the 2 treatment arms. However, the main aim when treating patients with metastatic prostate cancer is to achieve relief of symptoms. Our results have shown that Zoladex was more effective than stilboestrol in relieving symptoms, with a greater number achieving an earlier response.

The adverse events associated with stilboestrol were a common cause for withdrawal from treatment and this supports the findings of other authors (Veterans Administration Cooperative Urological Research Group, 1967; The Leuprolide Study Group, 1984), with cardiovascular side effects being the commonest reason. A subset of the patients from this study was investigated further and antithrombin III levels were found to be significantly lower and fibrinolytic activity was higher in the oestrogen-treated patients, providing a possible explanation for these adverse events (Emtage *et al.*, 1990).

The dose of stilboestrol, 3 mg per day divided into 3 doses, is the accepted regime in British urological practice following studies (Shearer *et al.*, 1973) which showed that serum testosterone was not as fully suppressed on 1 mg/day as on 1 mg 3 times daily in prostate cancer patients. Other workers (Bailar *et al.*, 1970) have used 1 mg per day and suggest that the clinical response rate is as good as at higher doses but with a lower incidence of side effects than when using 5 mg per day.

We have shown that Zoladex is as effective as oestrogen therapy for prostate cancer in terms of survival. It is associated with more subjective responses and a shorter time to achieve an objective response. We feel that Zoladex can be regarded as a medical alternative to surgical orchiectomy in the treatment of patients with prostate cancer who require hormonal manipulation.

Stilboestrol no longer has a place in the management of advanced prostate cancer when superior alternatives with less toxic side effects are available. However, as the majority of side effects to stilboestrol occur in the first 12 months, patients currently on stilboestrol treatment may continue on treatment without adverse effects expected to be reported.

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The data were stored on a local Area Vaxcluster in the CRC Trials Unit and analysed using the BMDP statistical package.

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Long-term Results of One-stage Scrotal Patch Urethroplasty

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Summary—Of 211 patients with urethral strictures undergoing one-stage dartos pedicled island patch urethroplasty between 1970 and 1987, 194 have been followed up from 3 to 20 years. There was 1 post-operative death (from hepatitis). During the period of follow-up, strictures recurred in 14 patients (7%), some of them as late as 15 years after an apparently successful urethroplasty. Calculi forming on hairs required treatment in 6 patients (3%) and it was necessary to revise a redundant skin pouch in 6.

Until recently the treatment of urethral strictures had hardly altered since the days of ancient Egypt or India and consisted almost entirely of dilatation or urethrotomy, either internal or external (Attwater, 1943). Today optical urethrotomy (Sachse, 1974) is the initial treatment of choice, but because it cannot be relied upon to yield a long-term cure (Johnston *et al.*, 1980; Chilton *et al.*, 1983) regular self-dilatation with the low-friction catheter has been reintroduced—an interesting return to ancient practice. Even so, there remain patients for whom urethrotomy is either impossible or has to be repeated very often: these patients need a more permanent remedy.

Many methods of urethroplasty have been tried in the past (Blandy, 1980). Excision and end-to-end anastomosis was described by Marion (1936) but few strictures lend themselves to this operation, with the notable exception of those which follow trauma.

Only when Johanson (1953) and Swinney (1953) adapted Denis Browne's two-stage hypospadias repair (Browne, 1936) to adult strictures were urologists provided with a procedure that could be applied to long and complicated strictures. At first, healing of the buried skin strip was often followed by fistulae but this was largely overcome by using a full-thickness tube of skin for the second stage rather than a buried strip (Turner-Warwick, 1960). Even so, adjustments and revisions were often needed between the first and second stages because of stenosis at the apex of the scrotal funnel.

These difficulties were mostly avoided by the ∩-shaped flap of Leadbetter (1960), especially if extended to the scrotal skin (Blandy *et al.*, 1968), but 2 operations were still needed, and the search for a reliable single-stage operation continued in urology as in plastic surgery. In both disciplines the solution was the myocutaneous flap.

A myocutaneous flap of skin on a pedicle of dartos muscle was first described in 35 adults and 6 children by Leadbetter and Leadbetter (1962). Later endorsed by Yaxley (1967) and Orandi (1968), by 1970 it had become the standard procedure in this department where it was easily adapted to the scrotal flap.

The concept proved to be very adaptable. Myocutaneous flaps based on the dartos could be used to patch the narrow urethra or, when rolled up into a tube, to replace a segment of the urethra in a single stage. The early results seemed to be encouraging (Orandi, 1967; Blandy and Singh, 1975; Gardiner *et al.*, 1978; Blandy, 1986) but, as with any surgical operation, there were complications.

The patch of scrotal skin continued to grow hair which could form stones, and it sometimes enlarged to form a redundant pouch. Reports of these

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sequelae led to a widespread belief that scrotal skin must never be used in urethroplasty, almost any other tissue being regarded as preferable (Quartey, 1985; Mundy and Stephenson, 1988) even at the price of a return to a two-stage procedure (Schreiter, 1984).

Since the dartos-pedicled scrotal skin patch remained the standard procedure in this department, it seemed timely to audit our results.

Patients and Methods

The series. A total of 211 one-stage island patch urethroplasties were performed between 1970 and 1987. Follow-up data were available from hospital records supplemented by direct contact with the patient by letter or telephone in 194 cases (92%); 11 patients had returned overseas for follow-up and the records of 6 other patients could not be located. The present study was based upon 194 patients followed up from 3 to 20 years (mean 5.5).

Indications for urethroplasty. All of these patients suffered from strictures which were impassable or had recurred after many previous urethrotomies and dilatations. There had been at least 1 previous attempt at urethroplasty in 51 patients (24%). When a stricture was situated upon the external sphincter, this was regarded as a contraindication to urethroplasty.

Age. The age range in this series was 12 to 85 years (mean 50). No age is exempt from urethral stricture.

Aetiology. The aetiology of the strictures in this series (Table 1) was similar to that in others. The "congenital" strictures were annular strictures in the bulbar urethra in young men who gave no history of trauma or previous urethritis, although neither of these aetiologies could be entirely excluded (Szemat-Nikolajenko and Cukier, 1978).

Two patients were included in this series who had undergone partial urethrectomy for localised carcinoma of the anterior urethra and were reconstructed with a tubed island patch.

Operative technique. The operative technique has been described elsewhere (Blandy, 1986), but a few minor modifications have been added in recent years.

In the early part of the series the scrotal incision was always an inverted ∪, but with the help of a weighted retractor (Fig. 1) it was often possible to gain all of the necessary access to the urethra through a simple transverse scrotal incision, which leaves an inconspicuous scar.

Table 1 Aetiology of 211 Urethral Strictures Treated by Dartos-pedicled Patch Urethroplasty

Aetiology	*No.*	*(%)*
Congenital	29	(13.7)
Hypospadias	16	(7.6)
Inflammatory		
Urethritis	33	(15 6)
Balanitis xerotica obliterans	5	(2.4)
Tuberculosis	1	(0.5)
Trauma		
Fractured pelvis	21	(9.9)
Fall-astride injury	19	(9.0)
Removal of urethral calculi	2	(1.0)
Radiotherapy	1	(0.5)
Post-operative		
Transurethral prostatectomy	18	(8.5)
Open prostatectomy	7	(3.3)
Instrumentation/catheters	14	(6.6)
Abscess and/or fistulas	4	(1.9)
Squamous carcinoma of urethra	2	(1.0)
Unknown or not recorded	39	(18.5)
Total	211	(100)

The stricture was posterior in 67% of patients and the skin patch was derived from the posterior rim of the incision or the tip of the flap (Fig. 2). In 20% it was anterior and the patch was made from the anterior edge of the incision (Fig. 3); 2 or more patches were required in the 13% with full length strictures.

To avoid fistulae in the shaft of the penis, when it was necessary to expose the anterior urethra the skin was sleeved back from a subcoronal incision and the penis everted into the transverse scrotal incision (Fig. 4).

No attempt was made to depilate the skin, previous experience having shown this to be futile. All patients were given prophylactic antibiotics for 5 days. A 16 F silastic catheter was kept in for 14 days.

Results

Early complications (Table 2)

The only post-operative death occurred in a man referred from elsewhere with active chronic hepatitis, whose stricture had required urethrotomy every 14 days: fulminant hepatic failure developed shortly after the operation and he died 4 weeks later, by which time his urethroplasty had healed.

All of the systemic complications occurred in men over the age of 60, except for 1 aged 56 who

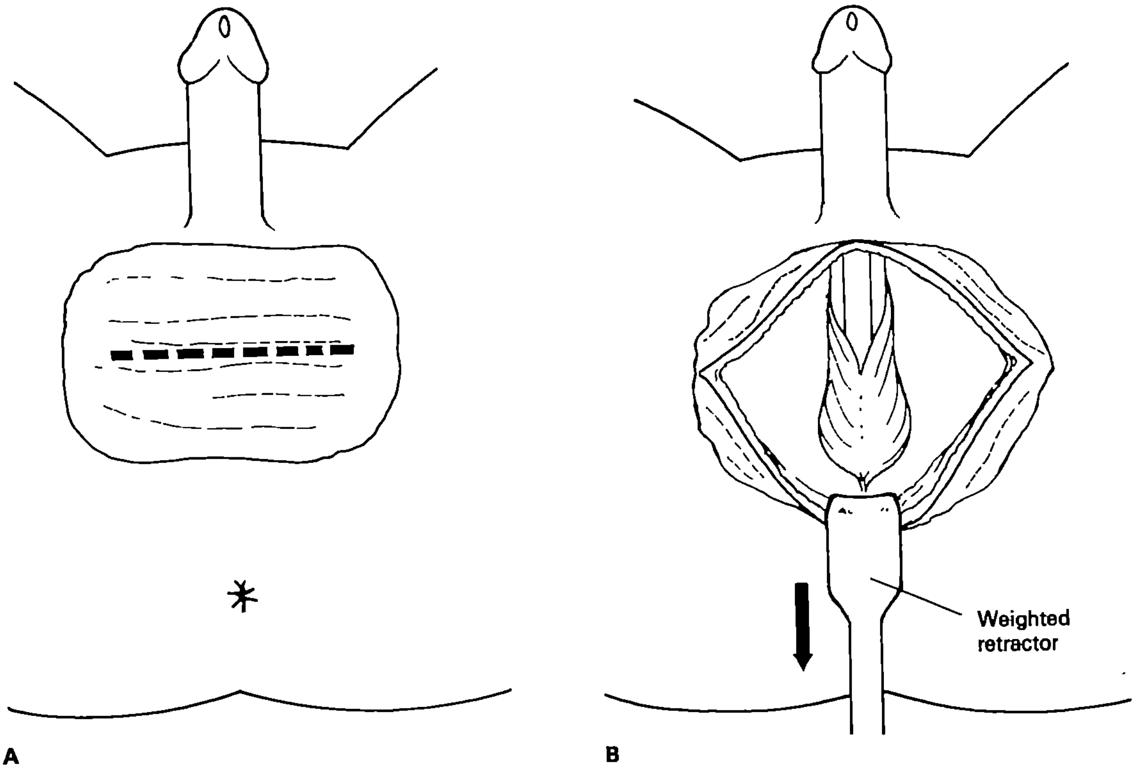

Fig. 1 (A) A transverse incision in the scrotum is found to give excellent access to most of the urethra, especially if (B) a weighted retractor is used to hold down the posterior part of the scrotum. This avoids the need for the ∩-shaped flap in the majority of cases.

developed a deep vein thrombosis 16 days after operation.

Epididymitis occurred in 9 men (4.5%). One haematoma required surgical evacuation.

Minor infections and delays in wound healing were common, as in most scrotal operations. Where the edge of the scrotal skin had been undermined to furnish the dartos pedicle for the patch a line of necrosis was seen in 11 patients (5%) but usually healed spontaneously. Major wound infection and dehiscence necessitated debridement and secondary suture in 8 cases (4%).

Fistulae were noted in 15 cases (7%) but usually closed within a few days; in 3 patients (1.4%) a second operation was needed at 6 weeks, 6 months and 18 months.

Complete necrosis of the patch occurred in 2 cases, giving a graft survival rate of 99%. Both patients underwent a successful second reconstruction. In 2 further patients, where the graft had been brought to the tip of the glans penis, the end of the graft appeared to undergo some necrosis, but after 1 week separation of some discoloured tissue left a completely healed anastomosis.

Long-term results

Deaths. In the 194 patients who could be followed up there were 17 deaths during the 20-year follow-up at a mean age of 66 years (range 37–87). Bladder carcinomas caused death in 4 patients, 1 of whom had a squamous carcinoma (Table 3).

Morbidity. During this prolonged follow-up no year went by without 1 or 2 patients returning each year with unexpected late complications (Table 4). Some of these men needed more than one procedure and are therefore listed several times. With the passage of time there was a steady increase in the total number of patients who came to need further intervention, and in the entire series, some of whom have been followed for more than 20 years, a total of 41 patients (21%) have required some additional procedure. To date some 79% have not, but it is likely that with increasing time some of these will also require further attention (Table 5).

Re-stenosis. The most common indication for

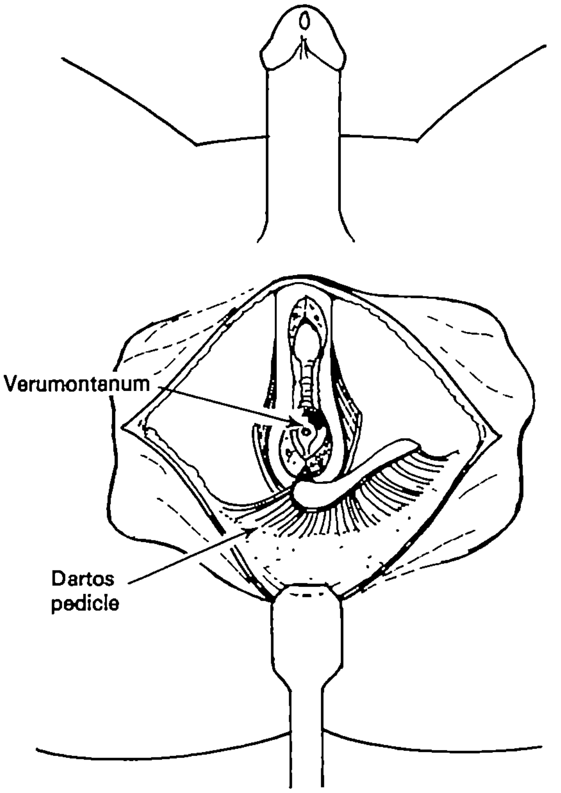

Fig. 2 The dartos-pedicled patch of scrotal skin is taken from the posterior edge of the transverse incision for strictures involving the bulbar urethra.

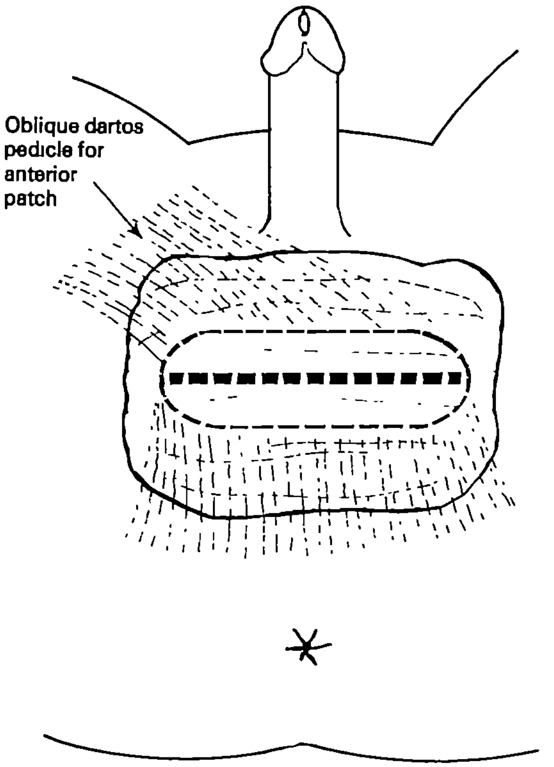

Fig. 3 In strictures involving the full length of the urethra 2 patches are made: one from the anterior part of the scrotum on a long oblique pedicle of dartos which allows it to be rotated up to the shaft of the penis and the other from the posterior edge of the transverse incision for bulbar strictures.

further intervention was recurrence of the stricture, which was seen in 14 patients (7%), nearly always at one or other end of the patch. This re-stenosis could occur a very long time after the urethroplasty: of the 26 patients who were followed up for between 10 and 20 years, 2 developed a new stricture after a symptom-free interval of more than 10 years.

Most of the new strictures were managed by optical urethrotomy but it was necessary to revise the urethroplasty in 4 cases (2%) where it was found that almost the entire patch of skin had undergone stenosis, and histological examination showed features of balanitis xerotica obliterans.

Two patients need more than 2 revisions. Both had strictures caused by major trauma: the first sustained a traumatic hind-quarter amputation with combined rectal and urethral injury; the other fell from a fifth floor balcony and had undergone 2 previous urethroplasties elsewhere, resulting in a mass of ectopic calcification around the stricture. Both eventually achieved a satisfactory result.

Pouches of skin. Dribbling after micturition was reported in 9 patients and was usually relieved by milking the urethra after voiding. In 6 patients (3%) the pouches became so big that they had to be revised within the first 3 years after the urethroplasty. It is likely that too large a patch of skin had been used in the first place, but sometimes the pouch formed upstream of a stenosis, and in 1 patient the dilatation was distal to the stenosis. It is easy to trim an excessively large pouch and if it is associated with stenosis the surplus skin can be used as a Y-V plasty (Fig. 5).

Hair and stones. The scrotal patch continues to grow hair which can always be seen at endoscopy. It causes trouble only if it leads to the formation of calculi. Hair-ball calculi were seen in 6 patients (3%), all of whom had stenosis downstream of the patch; 3 of them needed a further procedure to correct the stenosis after the calculi had been removed.

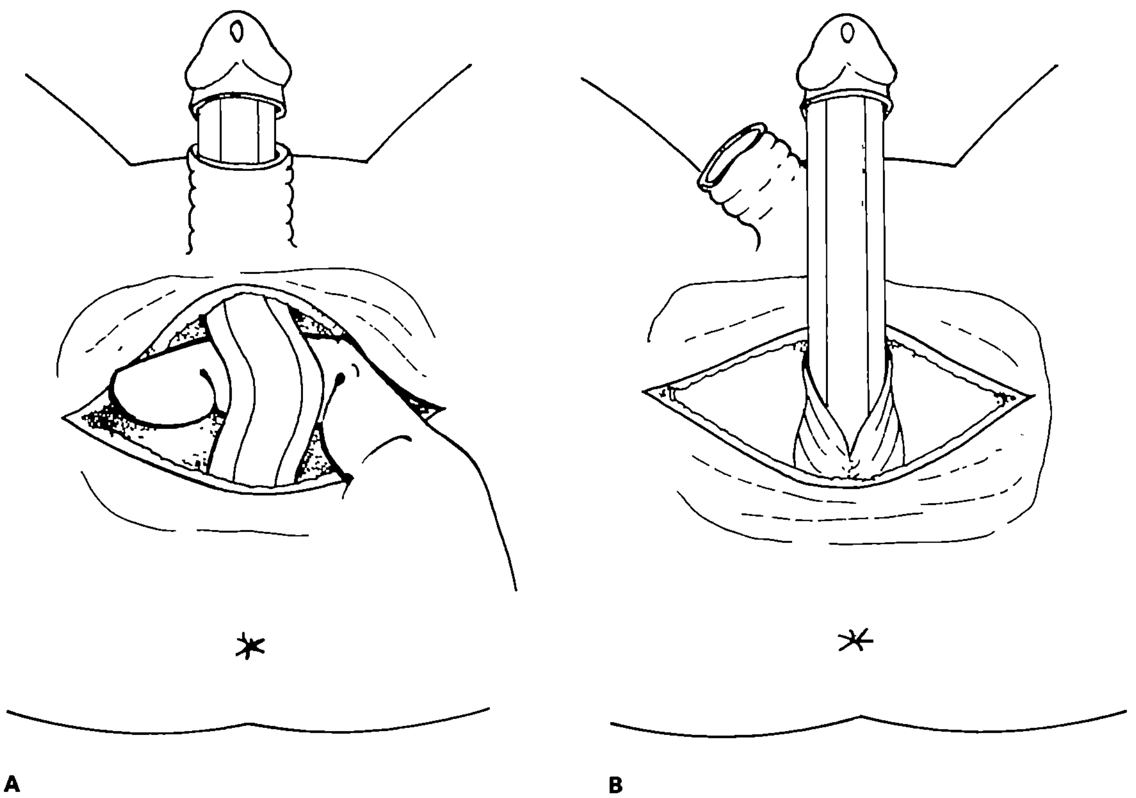

Fig. 4 To give access to the penile urethra without running the risk of a fistula, the skin of the penis is sleeved back by means of a circumferential incision behind the glans and the entire penis is then delivered through the transverse scrotal incision. This is particularly useful for reconstruction of the hypospadiac cripple.

Chordee. In 4 of the 64 patients in whom a pedicled patch had been placed in the anterior urethra the dartos pedicle appeared to tether the erect penis and cause chordee. After a few months the pedicles were divided and the chordee was corrected.

Impotence. Impotence was present in 9 patients who had pelvic injury before urethroplasty. In addition, in the course of the prolonged follow-up 2 elderly men reported that they had become impotent. No patient in this series who was potent before operation became impotent in the early years after his urethroplasty.

Incontinence. There were 4 patients with incontinence which dated from severe urethral trauma and which persisted after urethroplasty.

Previous prostatectomy had been performed in 25 patients. Two of these were incontinent since the time of the prostatectomy (performed elsewhere) and 4 others underwent prostatectomy at some time after their urethroplasty. Except for the 2 who were already incontinent, no others were made incontinent by the urethroplasty or the prostatectomy, but care was always taken not to use the technique for strictures at the external sphincter.

One curious symptom was noted by 4 patients (2%): they had a sensation of wetness on their scrotum but were in fact always quite dry when examined: it seems that they retained the sensation of wetness in the patch of scrotal skin within the urethral lumen.

Urinary infections. Severe urinary infections were see in 5% of patients in this series and episodes of acute epididymitis were noted in a further 3%. Urethrography often shows filling of dilated prostatic ducts and it seems probable that recurrent prostatitis is a long-term feature to be anticipated in any patient with a severe urethral stricture.

Table 2 Early Complications in 211 Dartos-pedicled Scrotal Skin Patch Urethroplasties

Complication	*No.*	*(%)*
Death (fulminant hepatic failure)	1	(0.5)
Chest infection	2	(1.0)
Cerebrovascular accident (full recovery)	1	(0.5)
Deep venous thrombosis	1	(0.5)
Pulmonary embolism	1	(0.5)
Epididymitis	9	(4.3)
Debridement and secondary suture	8	(3.8)
Haematoma requiring evacuation	1	(0.5)
Necrosis of graft	2	(1.0)
Fistulas		
temporary	15	(7.1)
requiring closure	3	(1.5)

Table 3 Deaths Occurring during 20-year Follow-up of 194 Urethroplasties

Cause of death	*No.*
Road traffic accident	1
Fire	1
Asbestosis	1
Acute abdomen (unspecified)	1
Ischaemic heart disease	2
Peripheral vascular disease	1
Cerebral tumour	1
Colonic carcinoma	1
Bladder cancer	
transitional cell	2
squamous cell	1
unspecified	1
Unknown cause	4
Total	17

Table 4 Late Complications in 194 Urethroplasties Followed up for 3–20 Years

Complication	*No.*	*(%)*
Re-stenosis	14	(7.2)
Impotence		
present before urethroplasty	9	(4.6)
late onset during follow-up period	1	(0.5)
Incontinence		
since previous prostatectomy	2	(1.0)
following major pelvic trauma	4	(2.1)
post-micturition dribble	9	(4.6)
sensation of wetness, but is dry	4	(2.1)
Urinary infections	10	(5.2)
epididymitis	6	(3.1)

Table 5 Further Procedures in 194 Patients Undergoing Dartos-pedicled Scrotal Skin Patch Urethroplasty

Further procedure	*No.*	*(%)*
For re-stenosis		
optical urethrotomy	14	(7.2)
return to dilatations	3	(1.5)
revision of urethroplasty	4	(2.1)
Reduction of redundant skin pouch	6	(3.1)
Division of dartos pedicles for chordee	4	(2.1)
Removal of urethral hair-ball calculus	6	(3.1)
Meatoplasty	4	(2.1)
Subsequent transurethral prostatectomy	3	(1.5)

Discussion

It is unnecessary to emphasise the advantages of a one-stage urethroplasty. Unfortunately, end-to-end anastomosis after excision of the stricture is seldom appropriate in patients who relapse after repeated optical urethrotomy, and for long strictures a substitute for urethral epithelium must be provided. A number of options have been suggested: they include pedicled skin from the scrotum or prepuce, free skin grafts, or bladder epithelium.

Free full thickness grafts of preputial skin have their advocates (Brannan *et al.*, 1976) but others have found them disappointing (Berger *et al.*, 1976) and it would be surprising if the graft survival rate were high in view of the mobility and the prevalence of infection in the perineum. Failure of a graft to take may be only a minor set-back in the treatment of a burn, but in urethroplasty it is a disaster. The results reported here should be compared with those published for free skin grafts (Berger *et al.*, 1976; Brannan *et al.*, 1976).

Using meshed split-skin may avoid hair growth at the cost of requiring a two-stage procedure (Schreiter, 1984; Lipsky, 1986).

Pedicled patches from the skin of the shaft of the penis or prepuce have been the subject of optimistic early reports; the long-term results are awaited with interest (Quartey, 1985; Mundy and Stephenson, 1988).

The use of free grafts of bladder epithelium is very interesting, but in children has been followed by some graft failure and re-stenosis (Duffy *et al.*, 1988). Animal studies would suggest that ectopic bone is likely to form in the tissues adjacent to such a graft (Blandy and McDonald, 1961).

It is well known that hair-bearing skin can give rise to calculi; in this series 3% formed stones, mostly between the sixth and tenth years of follow-up. So far none of the 26 patients followed for more

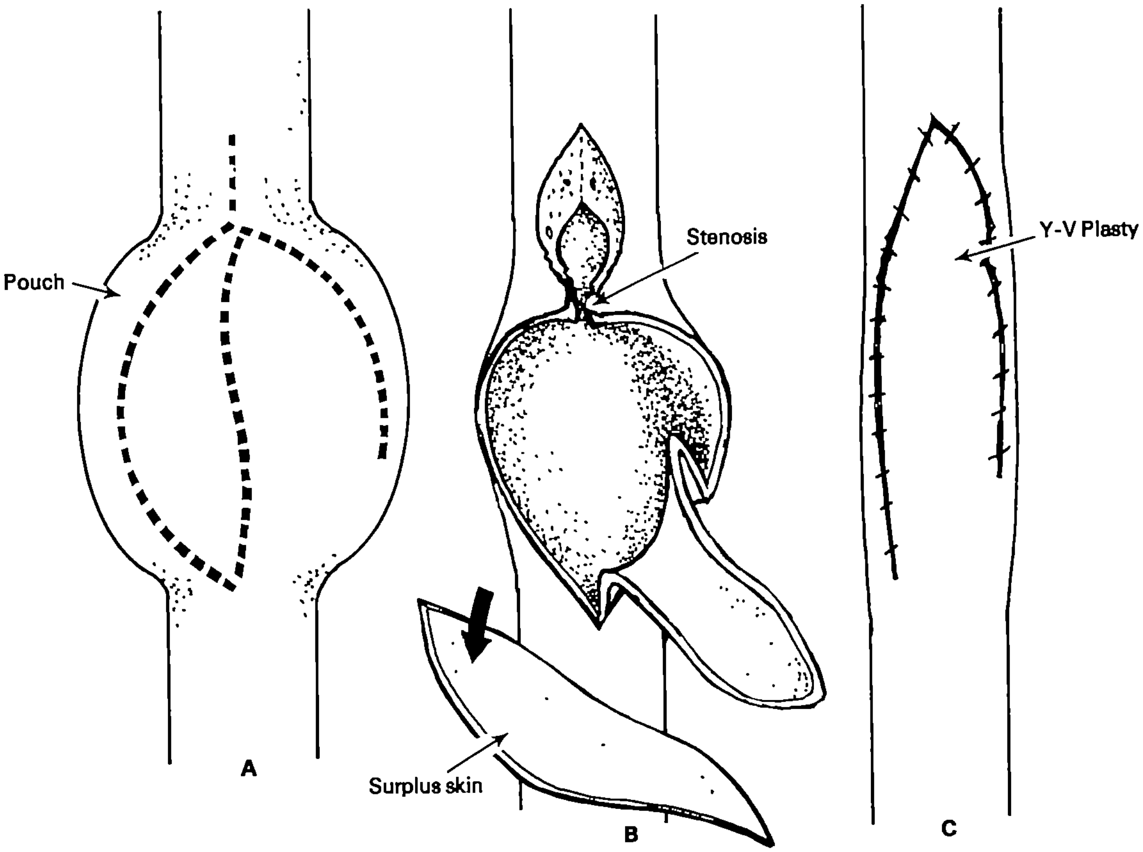

Fig. 5 (A) The redundant pouch from the previous urethroplasty is exposed through a short midline incision and the incision is planned to reduce the surplus pouch and provide a flap. (B) The flap has been prepared, the distal stenosis opened up and the redundant skin removed (C) The flap is advanced to open up the stenosis.

than 10 years has developed a stone. When they are shed, hairs are usually carried away in the flow of urine and the formation of a calculus seems to require stasis either from distal obstruction or in post-stenotic dilatation. A 3% chance of stone formation may be considered to be an acceptable price for the 99% viability of the graft.

Re-stenosis may occur after any form of urethroplasty. When it occurs in the scrotal skin there has often been a histological change similar to balanitis xerotica obliterans. Since BXO has a predilection for the prepuce, it will be interesting to see whether preputial grafts will also develop similar changes in the future.

Incontinence is a potential complication whenever there has been a previous prostatectomy, and in this series it was avoided by not offering urethroplasty when strictures involved the external sphincter. Fortunately such strictures were not common; even in high posterior urethral strictures there was usually a gap of about 1 cm downstream of the sphincter.

The occurrence of bladder cancer in the follow-up of men in this series is a cause for concern, especially as one of these patients had a squamous cell carcinoma, and squamous metaplasia is always present in the urethra upstream of a stricture (Colapinto and Evans, 1977; Houston, 1987). This is another reason for insisting on a careful follow-up of all patients with urethral strictures, whether they have undergone urethroplasty or not.

Our results show that while most patients may expect a good long-term result from scrotal patch urethroplasty, there is no room for complacency. The number who will require some further procedure is small but significant, and steadily increases year by year. The search for an ideal substitute for the urethra has not ended.

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Pre-operative Assessment of Peyronie's Disease Using Colour Doppler Sonography

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Summary—Colour Doppler ultrasonography was used to assess 39 patients with Peyronie's disease with a suspected organic cause for their impotence.

In 20 patients who complained of a uniform loss of erection, the impotence was likely to be functional in origin (90%) or occasionally venogenic (10%), the penile arterial blood flow being normal. However, patients who complained of distal flaccidity were likely to have an organic cause for their impotence (68%). This was due to proximal arterial disease (10%), plaque involvement of the distal vessels (37%), veno-occlusive dysfunction (5%) or to the soft glans syndrome (16%).

The erectile dysfunction associated with Peyronie's disease may be due to the deformity itself or to an impaired erection. It is often difficult to decide whether this is arterial, venogenic or functional in origin. Penile blood flow may be assessed accurately using duplex and colour Doppler ultrasound (Lue *et al.*, 1985; Quam *et al.*, 1989; Schwartz *et al.*, 1989; Shabsigh *et al.*, 1989) and Peyronie's plaques may also be seen ultrasonically (Hamm *et al.*, 1986).

This study used both modalities, allowing the relationship of the penile vessels to the Peyronie's plaque to be assessed, and the resultant type and cause of impotence to be diagnosed.

Patients and Methods

An assessment was made of 39 patients with Peyronie's disease who were clinically suspected of having an organic cause for their impotence. Their mean age was 53 years (range 31–69) and the average duration of the disease was 19 months.

The features noted from the clinical assessment were the description of the impotence (either uniform softness, distal flaccidity or glans softness), the angle of deformity and the presence of general vascular disease.

Following an intracavernosal injection of papaverine (40–80 mg), blood flow in the penile vessels was monitored at 3-min intervals using colour Doppler ultrasound (Acuson) with a 7.5 MHz probe. A vascular analysis of both cavernosal and dorsal arteries was performed, including the maximum systolic velocity (Vmax), the minimum end diastolic velocity (Vmin) and the pulsatility index. The vessels were then followed distally (Fig. 1) in order to assess patency and to observe any plaque involvement. Cavernosometry, using 80 mg papaverine, was performed in 10 patients where veno-occlusive dysfunction was suspected from the vascular analysis. A maintenance infusion >50 ml/min was taken as confirmatory of veno-occlusive dysfunction (Dickinson and Pryor, 1989).

The Doppler values indicative of a normal response to papaverine included a Vmax >30 cm/s and Vmin <8 cm/s at maximum rigidity (Benson and Vickers, 1989).

Results

Twenty patients complained of a uniform softness of erection (Table 1). All of the patients in this group had a normal Vmax (mean 62 cm/s, SD 23 cm/s) in the proximal vessels, with good flow

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Read at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

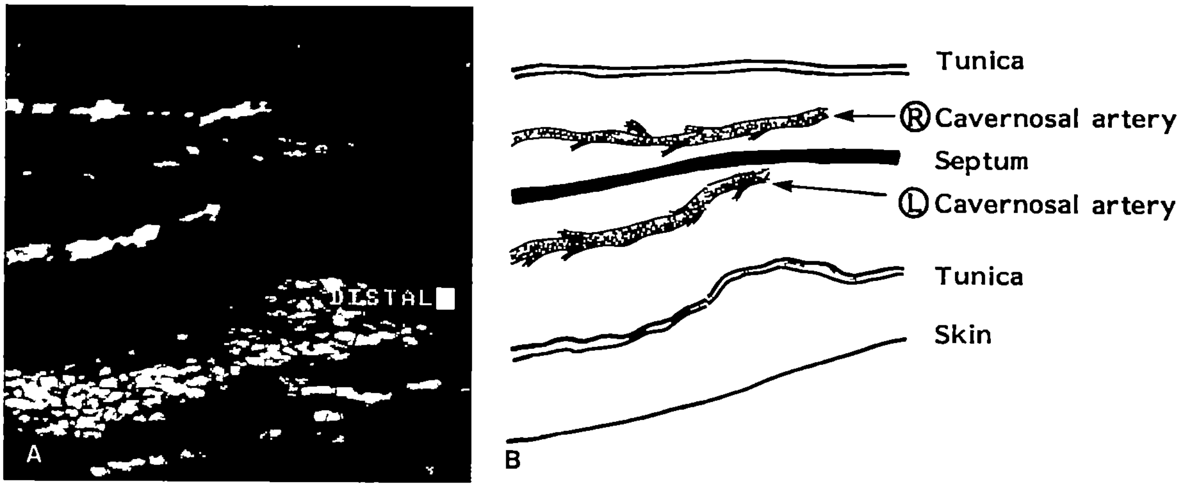

Fig. 1 Doppler mode showing distal penile vessels. (A) Actual image. (B) Schematic drawing.

distally in all but one case. Eighteen patients had a normal Vmin (mean 3.7 cm/s, SD 3.6 cm/s) with a good erectile response, their impotence therefore being functional in origin. Two patients had an abnormally high Vmin (>8 cm/s), suggestive of veno-occlusive dysfunction and confirmed by cavernosometry.

Nineteen patients complained of distal penile flaccidity (Table 2). Two had a low Vmax (<30 cm/s) due to proximal arterial disease, both with a known history of vascular disease. The remaining 17 patients had a normal Vmax (mean 46 cm/s, SD 12.4 cm/s) in the proximal vessels. However, in 7 patients there was reduced or absent flow in the distal penile vessels beyond the plaque, with a resultant true distal flaccidity. In these patients the Peyronie's plaque was extensive and surrounded the distal cavernosal vessels.

Table 1 Cause of Uniform Loss of Erection in Peyronie's Disease

Diagnosis	*No. of patients*
Psychogenic	17
Psychogenic + distal fibrosis	1
Venogenic	2
Arteriogenic	0
Total	20

Table 2 Cause of Distal Flaccidity in Peyronie's Disease

Diagnosis	*No. of patients*	*Doppler analysis*
Psychogenic	6	Vmax >30 cm/s, Vmin <8 cm/s
Arteriogenic—proximal	2	Vmax <30 cm/s
—distal	7	Vmax >30 cm/s Reduced or no distal flow
Venogenic	1	Vmax >30 cm/s, Vmin >8 cm/s
Soft glans	3	Vmax >30 cm/s, Vmin <8 cm/s
Total	19	

A diagnosis of a soft glans penis was made in 3 patients who complained of distal flaccidity. These patients had a normal Doppler analysis in the cavernosal vessels but had poorly seen dorsal arteries distally. As these patients had dorsal distal plaques, the soft glans was considered to be vascular in origin.

The plaque was easily seen in all patients (Fig. 2), predominantly on the dorsal aspect of the penis, and was calcified in 5 patients. The patients' description of the deformity was accurate to within 10° in 68% and to within 20° in 89% of cases.

Discussion

The incidence of erectile dysfunction associated with Peyronie's disease varies from 17 to 29% (Bystrom and Rubio, 1976; Stecker and Devine, 1984). This may be due to the deformity itself or to an impaired erection.

The impaired erection may be due to associated arterial disease, which occurs in 30% of patients (Chilton *et al.*, 1982), veno-occlusive dysfunction (Metz *et al.*, 1983; Gasior *et al.*, 1990), plaque extension into the cavernosal tissue, or it may be

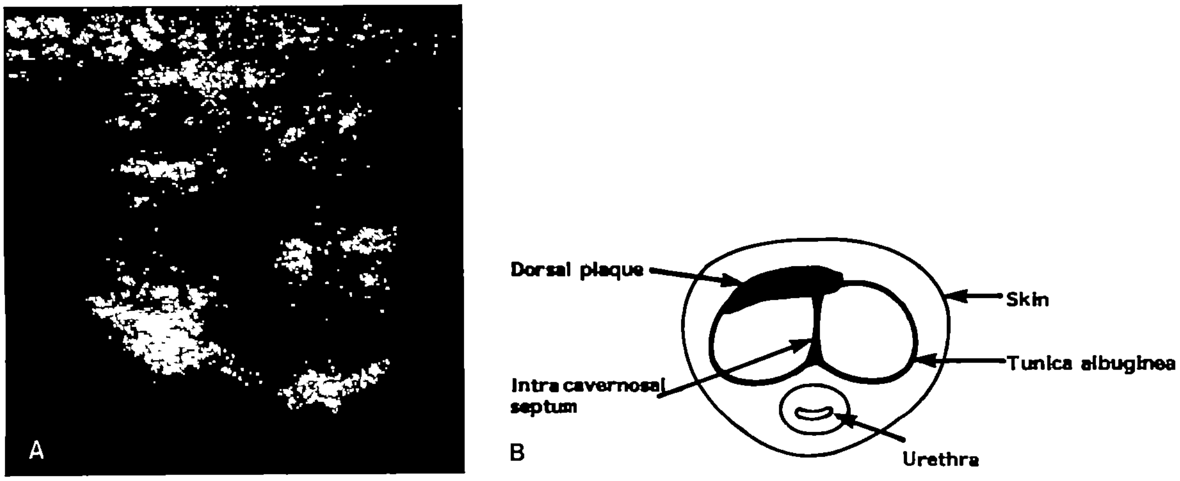

Fig. 2 Transverse ultrasonic view showing a dorsal plaque. (A) Actual image. (B) Schematic drawing.

functional in origin. However, it is not always easy to determine the aetiology of the erectile dysfunction.

The results show that the patients' symptoms reflect the aetiology of the dysfunction. In those who complain of a uniform loss of erection, the impotence is likely to be functional in origin (90%) or occasionally venogenic (10%). In this group the penile arteries were normal and so pharmacocavernosometry would therefore be a more appropriate first-line investigation.

Patients who complain of distal flaccidity are likely to have an organic cause for their impotence (68%). This may be due to proximal arterial disease (10%), when the patients have additional features of general vascular disease, or to distal arterial disease (37%). Here the distal vessels were involved in the fibrotic plaque and the blood flow beyond this was reduced or absent.

In 3 patients (16%) who complained of distal flaccidity, the "soft glans" syndrome was diagnosed from the clinical history and normal Doppler analysis. These patients had dorsal distal plaques which may cause this condition by invasion of the dorsal neurovascular bundle, as the dorsal penile vessels were not seen distal to the plaque.

It is in the group of patients who complain of distal flaccidity that Doppler assessment is most valuable. It allows differentiation of patients with psychogenic impotence and the "soft glans" syndrome, who can then have the deformity corrected if necessary, from those with true distal flaccidity which should be treated by a penile prosthesis.

The plaque is easily seen on ultrasound, allowing the size and consistency to be assessed, and this can subsequently be used to monitor treatment.

The patients gave an accurate description of their deformity, to within 10 to 20° in the majority of instances. It is, therefore, often unnecessary to obtain clinical confirmation of this, as has been advocated by some authors (Kelami, 1983; Desai and Gingell, 1987).

In conclusion, intracorporeal colour Doppler is a useful adjunct in the assessment of impotence associated with Peyronie's disease, especially if the complaint is of distal flaccidity, where an organic cause is likely.

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Contralateral Testicular Blood Flow in Unilateral Testicular Torsion Measured by the ^{133}Xe Clearance Technique

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Summary—Contralateral testicular blood flow was measured by the intratesticular injection of ^{133}Xe in 9 controls (Group 1) and in 34 adult male albino rats with experimentally induced left testicular torsion. In Group 2 (n = 9) testicular torsion was maintained for 3 h; in Group 3 (n = 7) torsion was maintained for 9 h and in Group 4 (n = 10) for 15 days. In Group 5 (n = 16) torsion was maintained for 9 h in 8 rats and the sera were given to 8 normal animals.

In Groups 3, 4 and 5 there was a significant increase in contralateral testicular blood flow on the fifteenth day. This increase may be the cause of contralateral testicular damage in prolonged unilateral testicular torsion.

The mechanism responsible for contralateral testicular damage in unilateral testicular torsion has not yet been established and controversy surrounds the results of studies on autoimmunisation (Mastrogiacomo *et al.*, 1982; Kogan *et al.*, 1986; Mazurkiewicz, 1986; Ryan *et al.*, 1988) and histopathological changes in the contralateral testis (Chakraborty *et al.*, 1986; Jhunjhunwala *et al.*, 1986; Turner, 1987). A decrease in contralateral testicular blood flow during short-term torsion has been reported by Tanyel *et al.* (1989).

We report an experimental study in rats to evaluate the long-term effect of unilateral testicular torsion on the contralateral testicular blood flow by using the ^{133}Xe washout technique.

Materials and Methods

Fifty-eight adult male albino rats were divided into 5 groups. Surgical procedures were performed via left scrotal incisions under intraperitoneal pentobarbital anaesthesia. Seven rats were lost during the study and are not included in the results.

Group 1 (n = 9) served as controls and underwent sham operations; 15 min, 7 days and 15 days later, the contralateral testicular blood flow was measured by intratesticular injection of 0.1 ml (100 μCi) ^{133}Xe.

In Group 2 (n = 9), 720° left testicular counterclockwise torsion was maintained for 3 h. The contralateral testicular blood flow was measured 15 min after torsion, immediately before and after detorsion, and 7 and 15 days post-operatively.

Left testicular torsion was maintained for 9 h in Group 3 (n = 7), followed by the same procedure as in Group 2.

In Group 4 (n = 10), torsion was maintained and the contralateral testicular blood flow was measured on the seventh and fifteenth post-operative days.

In Group 5 (n = 16), left testicular torsion was maintained for 9 h in 8 rats and the sera of these animals were then injected into 8 normal rats. The right testicular blood flow of these normal rats was measured on the seventh and fifteenth post-operative days.

Data were analysed for differences between groups using the Wilcoxon and Mann Whitney U tests.

Measurement of blood flow

Testicular blood flow was measured by the ^{133}Xe clearance technique (Wax, 1971). The rats were

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placed in the prone position over the gamma camera (Toshiba GCA 501) and 100 to 200 μCi ^{133}Xe in 0.1 ml physiological saline solution were injected into the testis. The data were stored on the computer disc of the gamma camera for further processing. Sequential 20-s frames were collected for 15 min. The testicular washout curve was generated using a suitable region of interest. The half-time of the exponential curve was calculated and testicular blood flow in ml/100 g/min was estimated using the following formula:

$$\text{flow (ml/100 g/min)} = \frac{0.693 \times \lambda \times 100}{T_{1/2}}$$

Generally, λ (partition coefficient) was taken around 0.85. Haematocrit was measured in all cases and the appropriate correction was made.

Results

In Group 2 rats, contralateral testicular blood flow increased 15 min after torsion but a decrease close to control values was seen immediately after detorsion and on the fifteenth day. In Group 3, contralateral testicular blood flow decreased close to control values immediately after detorsion. This was followed by a significant increase on the seventh and fifteenth days ($P < 0.05$) (Fig. 1). Blood flow in Group 4 rats demonstrated a significant increase on the fifteenth day ($P < 0.05$). In Group 5 animals there was a significant increase in the contralateral testicular blood flow 15 min after injection and also on the seventh and fifteenth days ($P < 0.05$) (Fig. 2). Figure 3 shows the contralateral testicular blood flow curves.

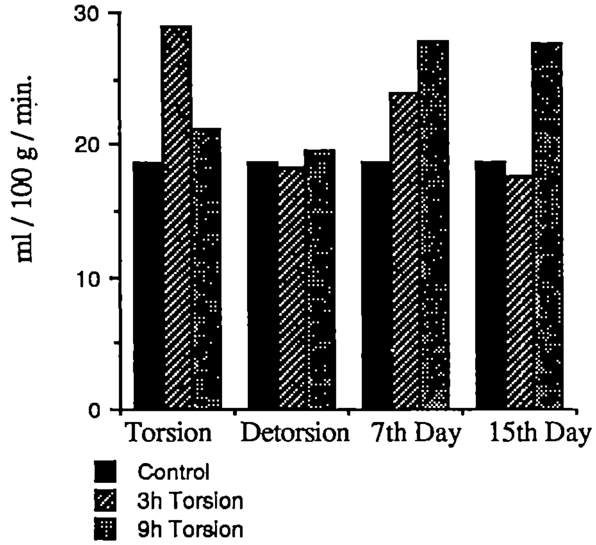

Fig. 1 Changes in contralateral testicular blood flow in Groups 2 and 3.

Discussion

The testes require a regular blood flow in order to maintain their normal spermatogenic function. In patients with varicocele, alterations in testicular

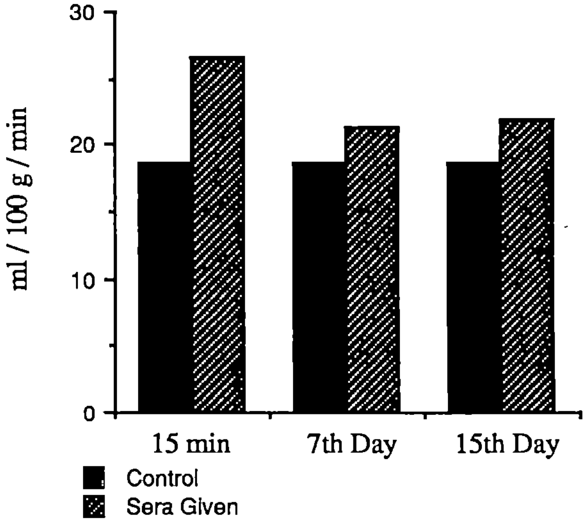

Fig. 2 Changes in contralateral testicular blood flow in Group 5 (received sera)

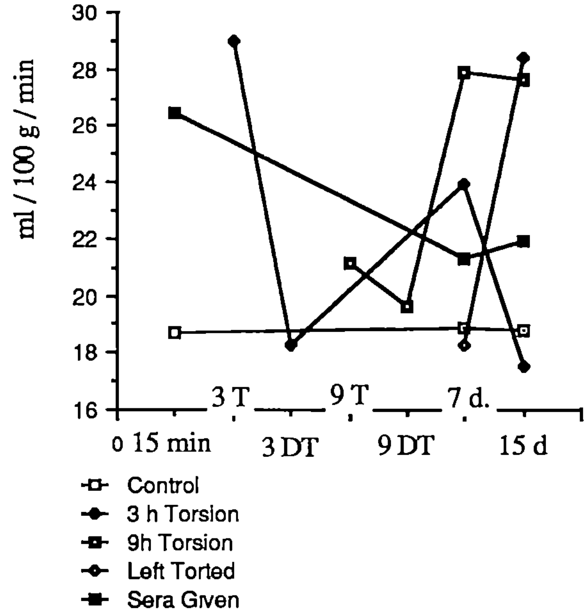

Fig. 3 Contralateral testicular blood flow curves (Groups 1–5).

blood flow (*e.g.* venous reflux and stasis) may result in infertility (Heinz *et al.*, 1980).

Experimentally induced varicoceles in rats and dogs led to changes in testicular histology and a significant bilateral increase in testicular blood flow and temperature (Saypol *et al.*, 1981). An increase in testicular temperature is known to cause spermatogenic disturbance both in man and in animals (Robinson *et al.*, 1968; Harrison, 1975).

In the present study, a significant increase in contralateral testicular blood flow was found on the fifteenth day in Groups 3, 4 and 5. It is thought that increased blood flow followed by an increase in temperature may cause contralateral testicular damage in prolonged unilateral testicular torsion.

Of particular interest was the observation that in Group 5 rats (who received sera), the increase in right testicular blood flow was maintained for 15 days. This suggests the existence of a vasoactive mediator responsible for the increase. A further experimental study is planned to evaluate possible vasoactive mediators and changes in intratesticular temperature.

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Complete Resolution of a Large Seminal Vesicle Cyst—Evidence for an Obstructive Aetiology

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Summary—Seminal vesicle cysts may arise from inflammation or obstruction of the seminal vesicle or from embryological remnants such as the müllerian duct. Surgical removal has been proposed as the treatment of choice.

A 19-year-old boy presented with abdominal pain and constipation. Investigations revealed a 14-cm multiloculated cyst arising from the right seminal vesicle and a small stone lodged at the orifice of the ipsilateral ejaculatory duct. Following endoscopic removal of the stone the mass decreased in size considerably and 2 months later transrectal ultrasound and magnetic resonance imaging showed normal seminal vesicles and no evidence of the cyst.

This case strongly supports an obstructive aetiology for this cyst and we would suggest that, in similar cases, full assessment of the ejaculatory apparatus should be carried out to exclude an obstructive cause before embarking on major surgery.

Cysts in the seminal vesicles were considered rare, but are now seen with increasing frequency with modern pelvic imaging modalities. Their aetiology is unclear but, when requiring treatment, most reports suggest that they should be resected by an abdominal or perineal approach. This is a major surgical undertaking, particularly in patients with benign disease. Our experience suggests that a large cyst in the seminal vesicle can develop secondary to obstruction at the ejaculatory duct; the treatment in this case was endoscopic and not excisional.

Case Report

A 19-year-old boy presented via the accident and emergency department with a 6-week history of lower abdominal discomfort and constipation. Abdominal examination revealed a soft, non-tender mass arising from the pelvis and on rectal examination there was a fluctuant mass above the prostate.

Plain abdominal X-ray showed a large soft tissue mass arising from the pelvis. Transabdominal ultrasound (Fig. 1) and CT scan (Fig. 2) confirmed the presence of a 14-cm multiloculated cystic mass between the bladder and rectum. Intravenous urography showed a moderate right hydronephrosis and a normal left upper tract. Transrectal ultrasound was performed in order to exclude prostatic pathology and to examine the seminal vesicles. This showed the mass to be directly superior to the prostate but the seminal vesicles could not be seen. The ejaculatory ducts did not appear dilated but a 0.5-cm cyst was seen in the region of the right duct near the verumontanum.

Cystoscopy revealed marked elevation of the trigone and posterior wall of the bladder by the mass and, on examination of the prostatic urethra, a small stone was seen protruding from the orifice of the right ejaculatory duct. This was dislodged endoscopically with a urethrotomy knife.

Two weeks later he was readmitted for formal exploration of the mass. However, on examination, the mass had decreased in size considerably. This was confirmed by repeat transrectal ultrasound (Fig. 3). Laparotomy was, therefore, deferred and vasography performed to assess further the involved seminal vesicle. On the right the vas deferens and ejaculatory duct appeared normal but the seminal vesicle was moderately dilated. On the left the vas was narrow and could not be cannulated.

Two months later transrectal ultrasound and a magnetic resonance imaging scan showed no evidence of the

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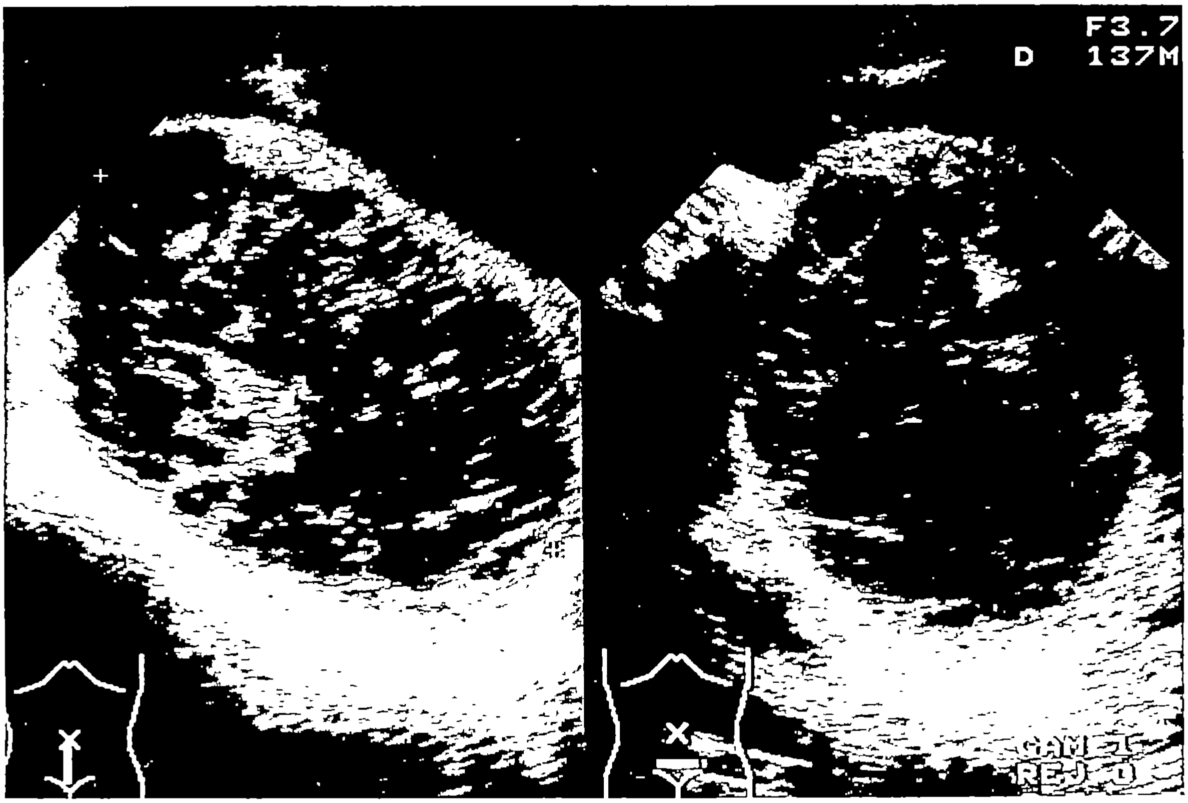

Fig. 1 Transabdominal ultrasound scan showing the large multiloculated cyst compressing the bladder anteriorly.

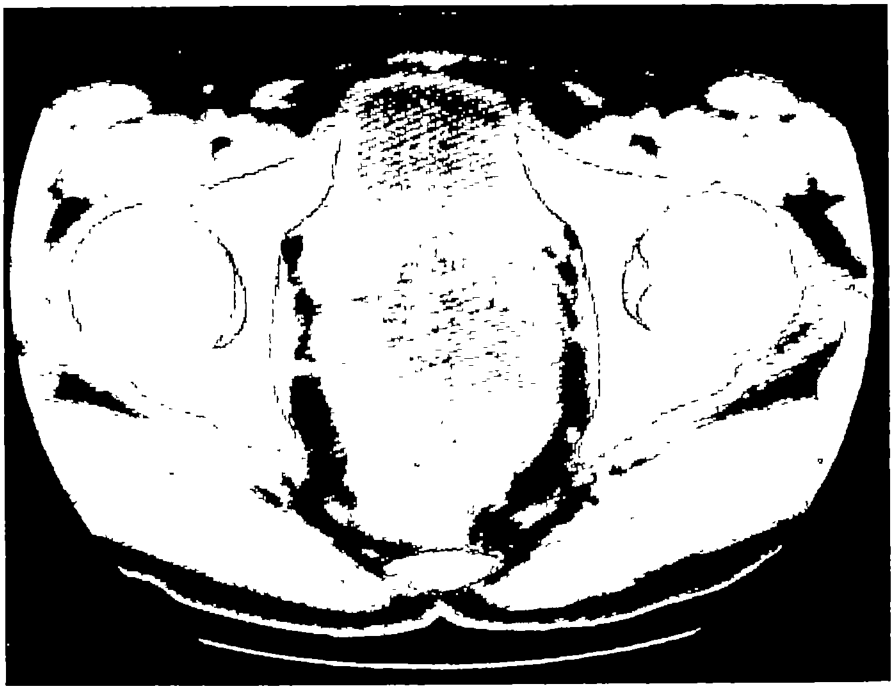

Fig. 2 CT scan of the pelvis showing the cyst lying between the bladder anteriorly and rectum posteriorly.

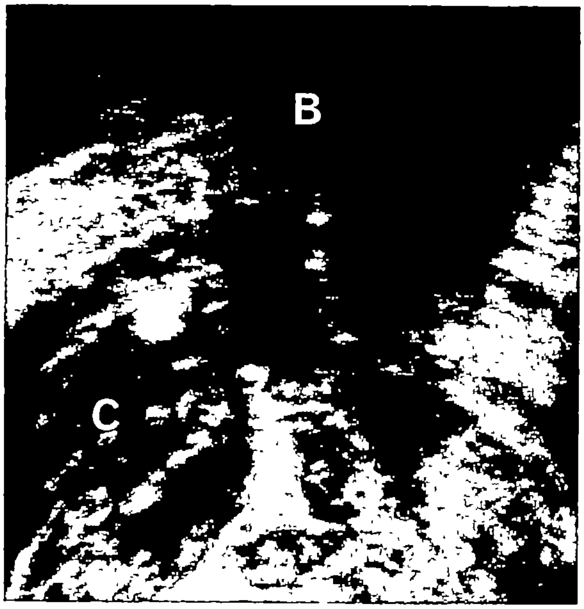

Fig. 3 Transrectal ultrasound. Sagittal scan 2 weeks after removal of the ejaculatory duct stone. The cyst (C) has decreased in size but still indents the posterior bladder wall (B).

cyst and normal seminal vesicles but the small cyst in the region of the right ejaculatory duct persisted (Fig. 4). On review 1 year later the ultrasound appearance was unchanged.

Discussion

Both benign and malignant tumours of the seminal vesicle have been reported rarely (Buck and Shaw, 1972; Williamson, 1978; Heaney *et al.*, 1987; Bullock, 1988). Malignant tumours are often advanced at first presentation and are associated with a poor prognosis (Lazarus, 1946). Although small cysts of the seminal vesicles are now seen relatively commonly with transrectal ultrasound, large cysts are much less common, with fewer than 100 cases reported in the literature. They are thought to arise as a result of inflammation or obstruction of the seminal vesicle (Heaney *et al.*, 1987; Bullock, 1988) or from remnants of the müllerian duct (Ornstein and Kershaw, 1985). Although in the case presented here no tissue was examined histologically, the clinical course strongly suggests that the cyst was due to obstructive dilatation rather than to a benign neoplasm.

Approximately two-thirds of cases reported are associated with ipsilateral renal agenesis (Heaney *et al.*, 1987) and more rarely with absence of the testis (Das and Amar, 1980) and absence or atresia of the vas deferens (Walker and Bowles, 1968; Ornstein and Kershaw, 1985). One case of absence of the contralateral vas has been reported (Girgis *et al.*, 1968). In our case the left vas was narrow and could not be cannulated but no further investigation was performed to establish its anatomy.

The majority of seminal vesicle cysts are small (<5 cm) and are either asymptomatic or present with infective or irritative urinary symptoms. Large cysts may present with symptomatic obstruction of the bladder and/or bowel. Because of their rarity, management principles have not been established. Lawson and MacDougall (1965) suggested that marsupialisation or aspiration of the cyst was unlikely to be successful because of their multilocular nature, and the generally accepted management appears to be resection by an abdominal or perineal approach (Stewart and Nicoll, 1949; Bullock, 1988). However, the case reported by Bullock (1988), where intra-operative rupture of the cyst resulted in a pseudomyxoma peritonei type of picture, emphasises one potential complication of abdominal excision.

Calculi within the ejaculatory duct have been identified with the aid of modern multiplanar transrectal ultrasound probes and this is now a

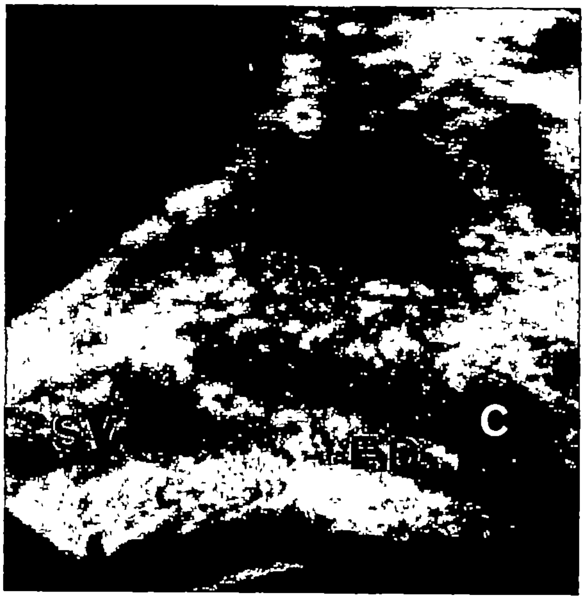

Fig. 4 Transrectal ultrasound. Sagittal scan 2 months later showing complete resolution of the cyst. The right seminal vesicle (SV) and the small cyst (C) in the region of the ejaculatory duct (ED) can be seen.

recognised cause of haematospermia (Etherington *et al.*, 1990). Obstruction of the duct by a calculus with the development of a large seminal vesicle cyst has not previously been reported, although an association between these cysts and ejaculatory duct obstruction was proposed by Heaney *et al.* (1987).

In the case reported here, complete resolution of the cyst occurred over a 2-month period following removal of a calculus from the orifice of the ipsilateral ejaculatory duct. Although there is no direct evidence of a causal relationship, it seems likely that removal of the obstruction resulted in gradual deflation of the dilated seminal vesicle and the return of a normal ultrasonic appearance. In view of this we would suggest that, in any patient with a large seminal vesicle cyst, full assessment of the ejaculatory apparatus should be carried out by either transrectal ultrasound or vasography in order to exclude an obstructive cause before embarking on major surgery.

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Survey of Mycobacteria Isolated from Urine and the Genitourinary Tract in South-East England from 1980 to 1989

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Summary—Between 1980 and 1989, the Public Health Laboratory Service Regional Tuberculosis Centre, Dulwich, received cultures of mycobacteria isolated from urine and the genitourinary tract of 1392 new patients: 803 isolates were members of the tuberculosis complex (753 *M. tuberculosis*, 45 *M. bovis*, 4 *M. africanum*) and 589 were various species of environmental mycobacteria. The incidence of the latter isolations varied by region and by year and, with 17 exceptions (13 from endometrial curettings, 2 from hydrocele fluid, 1 from a scrotal abscess and 1 from a kidney), all isolations of environmental mycobacteria were from urine; very few of them appeared to be clinically significant. Those that could be significant included 1 isolate from a kidney, 1 from a post-renal transplant patient and 4 from patients with AIDS, 3 of whom had disseminated mycobacterial disease. Reports of clinically significant isolations of environmental mycobacteria from the genitourinary tract are reviewed.

The genitourinary tract is a common site of non-pulmonary tuberculosis. A survey conducted in South-East England between 1977 and 1983 showed that 527 of 6850 strains of *Mycobacterium tuberculosis* isolated from European patients and 122 of 3850 strains isolated from patients of Indian subcontinent (ISC) ethnic origin were from the genitourinary tract (Grange *et al.*, 1985). More recently, it has been shown that an unexpectedly high proportion of cases of tuberculosis due to *M. bovis* in British patients from South-East England involve the genitourinary tract: 43 of 167 (26%) (Yates and Grange, 1988).

Other mycobacterial species (variously termed environmental, atypical or opportunist) may also be isolated from urine, although genitourinary disease due to these species is extremely rare. These species are widely distributed in the environment and are particularly found in water, including piped water supplies. Thus most isolations of these species result from their chance presence, possibly as transient commensals, in the lower urethra or on the external genitalia. In addition, there have been a few clusters of isolations resulting from collection of urine in contaminated containers. It is often stated in textbooks that *M. smegmatis*, a rapidly growing, thermophilic, saprophytic mycobacterium, is particularly common in urine, but this has not been our experience.

The purpose of this study was to determine the nature of, and changing trends in, the isolation of mycobacteria from urine and the genitourinary tract in South-East England between 1980 and 1989.

Materials and Methods

About 95% of all mycobacteria isolated in South-East England are referred for identification and drug sensitivity testing to the Public Health Laboratory Service Regional Tuberculosis Centre, at Dulwich (Jenkins *et al.*, 1985). Information on the age and sex of the patient is usually supplied by

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the referring laboratory. Patients were divided into apparent European, Indian subcontinent, African and Far East ethnic groups on the basis of their names.

Tubercle bacilli were divided into the classical and Asian types of *M. tuberculosis, M. bovis* and *M. africanum* types I and II according to their oxygen preference (aerobic or microaerophilic), nitratase activity and susceptibility to pyrazinamide and thiophen-2-carboxylic acid hydrazide (Collins *et al.*, 1982, 1985).

Other mycobacterial species (environmental, opportunist or "atypical") were identified by cultural and biochemical tests supplemented, when necessary, by lipid chromatography (Collins *et al.*, 1985; Jenkins *et al.*, 1985). This system does not identify all isolates at species level but is designed to separate them into clinically meaningful groups.

Except where stated, all data were analysed on the basis of one isolate per patient.

Results

During the 10-year study period, 1392 patients with mycobacteria isolated from urine or the genitourinary tract were registered.

Tuberculosis complex. Cultures from 803 patients were identified as being members of the tuberculosis complex: 753 *M. tuberculosis* (650 classical and 103 South Indian), 45 *M. bovis* and 4 *M. africanum* (all type I). One strain of BCG was isolated from the scrotum of a European man who had been treated for bladder carcinoma by local application of BCG.

The ethnic origin and sex of the patients are shown in Table 1. Most isolates were from European patients and males predominated. The annual isolation rates of these strains according to the ethnic origin of the patients are shown in Table 2. The TCH-sensitive South Indian type of *M. tuberculosis* occurred more frequently in the ISC group, while *M. bovis*, with one exception, was isolated only from the European group (Table 3). The anatomical origins of the isolates are shown in Table 4. The origins were similar in the 4 ethnic groups and the majority of isolations were from urine.

Environmental mycobacteria. Environmental species were isolated from 589 individuals. With 17 exceptions, all isolations were from urine. The species or groups isolated are shown by year in Table 5. The most frequently isolated mycobacteria were *M. xenopi* and slow-growing scotochromogens. Some variations in the annual incidence of isolates were evident, especially in the case of *M. xenopi*, which reached a peak in 1983 and subsequently showed a fairly steady decline. Thermophilic rapid growers (the smegmatis/phlei group) were isolated only during the first 4 years of the study and the 6 strains were isolated at 6 different hospitals. In 5 cases, 2 different species were isolated from the urine of the same person. In 19 cases the patient also had tuberculosis (11 pulmonary and 8 non-pulmonary).

Four patients were known to have AIDS. In one, *M. xenopi* was isolated from urine only; in another, *M. kansasii* was also isolated from bone marrow and the remaining 2 patients had disseminated *M. avium-intracellulare* infection.

In one instance, *M. fortuitum* was isolated from the urine of a renal transplant recipient.

Table 1 Ethnic Origin and Sex of Patients from whom Mycobacteria of the Tuberculosis Complex and Environmental Mycobacteria were Isolated

Ethnic origin	*Tuberculosis complex*		*Environmental*	
	*Total (%)**	*Male (%)†*	*Total (%)**	*Male (%)†*
European	558 (69.5)	335 (60)	378 (64.2)	146 (39)
ISC	215 (26.8)	127 (59)	201 (34.1)	83 (44)‡
African	5 (0.6)	1	6 (1.0)	4
Far East	25 (3.2)	15 (60)	4 (0.7)	1**
Total	803 (100)	478 (59)	589 (100)	234 (41)

* Percentage of all isolates within the bacterial group.

† Percentage of males within each ethnic group.

‡ Sex unknown in 11 cases.

** Sex unknown in 1 case.

Table 2 Annual Numbers and Ethnic Origins of Newly Registered Patients from whom Members of the Tuberculosis Complex were Isolated

Ethnic origin	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*	*1987*	*1988*	*1989*	*Total*
European	88	89	74	76	38	41	31	47	36	38	558
ISC	26	21	21	19	14	28	28	15	18	25	215
African	1	–	–	1	–	–	–	–	1	2	5
Far East	1	3	4	3	–	3	4	4	2	1	25
Total	116	113	99	99	52	72	63	66	57	66	803

Table 3 Species within the Tuberculosis Complex According to the Ethnic Origins of the Patients from whom they were Isolated

	M. tuberculosis				
Ethnic group	*Classical (%)*	*Asian (%)*	*M. bovis*	*M. africanum type I*	*BCG*
European	457 (70.3)	54 (52.4)	44	2	1
ISC	169 (26)	43 (41.7)	1	2	–
African	4 (0.6)	1 (1)	–	–	–
Far East	20 (3.1)	5 (4.9)	–	–	–
Total	650	103	45	4	1

Table 4 Source of Organism of the Tuberculosis Complex According to Ethnic Origin of the Patient

	Ethnic origin			
Source	*European (%)*	*ISC (%)*	*African*	*Far East*
Urine	470 (84.2)	177 (82.3)	4	20
Kidney tissue	14 (2.5)	3 (1.4)	–	2
Bladder tissue	5 (0.9)	3 (1.4)	–	–
Male genital	41 (7.3)	16 (7.4)	1	2
Female genital	27 (4.8)	16 (7.4)	–	1
Other*	1 (0.2)	–	–	–
Total	558 (100)	215 (100)	5	25

* Wound swab, post-prostatectomy.

Most isolations from urine were made on only 1 occasion: in 4 cases there were 2 isolations (2 scotochromogens, 1 *M. fortuitum* and 1 *M. avium-intracellulare*) and in another 4 cases there were 3 isolations (3 *M. xenopi* and 1 *M. chelonae*). In most cases the multiple isolations were made at close intervals and were probably not clinically significant. A possible exception was the isolation from an 8-year-old boy of *M. avium-intracellulare* on 2 occasions, 1 month apart.

The 17 cases in which environmental mycobacteria were isolated from sites other than urine, including 13 isolations from endometrial curettings, are listed in Table 6. With the possible exception of the isolate of *M. fortuitum* from a kidney, these appear to represent casual isolates. Two patients with isolations of scotochromogens from uterine curettings were from the same hospital in successive years (1983, 1984). Similarly, 2 patients with *M. chelonae* isolated from this site were from the same hospital in successive years (1982, 1983).

The species of mycobacteria isolated at hospitals from which 10 or more strains were received are shown in Table 7. Distinct variations between hospitals in the relative numbers of the various species isolated were evident. In some hospitals (2, 3 and 28) *M. xenopi* dominated, whilst in others (1, 7, 37 and 67) most isolates were slow-growing scotochromogens. A few other small clusters of hospital-associated isolations were apparent and some were also clustered in time; *e.g.* the 4 strains of MAI from hospital 29 were isolated between 1985 and 1986. Though predominant throughout, neither *M. xenopi* nor the slow-growing scoto-

Table 5 Sites of Isolation, other than Urine, of Environmental Mycobacteria

Year	*Ethnic origin*	*Sex*	*Age (years)*	*Site*	*Organism*
1980	ISC	F	33	Kidney	*M. fortuitum*
1981	ISC	M	–	Hydrocele	*M. chelonae*
1989	European	M	73	Hydrocele	Scotochromogen
1983	European	M	46	Scrotal abscess	Scotochromogen
1980	European	F	41	Endometrium*	*M. avium-intracellulare*
1981	European	F	33	Endometrium*	Scotochromogen
1981	European	F	26	Endometrium*	Scotochromogen
1982	ISC	F	23	Endometrium*	*M. chelonae*
1983	ISC	F	24	Endometrium*	*M. chelonae*
1983	European	F	31	Endometrium*	*M. kansasii*
1983	European	F	27	Endometrium*	Scotochromogen
1984	European	F	32	Endometrium*	Scotochromogen
1986	European	F	22	Endometrium*	*M. fortuitum*
1986	European	F	36	Endometrium*	Non-chromogen†
1986	ISC	F	26	Endometrium*	*M. chelonae*
1987	European	F	24	Endometrium*	Scotochromogen
1989	European	F	–	Endometrium*	Scotochromogen

* All endometrial isolates were from uterine curettings.
† An unidentified psychrophilic strain.

Table 6 Annual Isolation Rate of the Species or Groups of Environmental Mycobacteria (based on one isolate per patient)

	Year										
Species or group	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*	*1987*	*1988*	*1989*	*Total*
M. xenopi	20	27	39	33	28	13	5	6	3	2	176
Scotochromogen–SG	27	31	28	25	15	26	9	13	20	17	211
M. kansasii	7	5	3	3	1	4	3	3	3	2	34
MAI	2	1	2	1	2	1	4	1	1	2	17
M. simiae	–	1	–	–	–	–	–	–	–	–	1
Terrae group	2	–	–	1	1	–	–	–	–	–	4
M. fortuitum	10	7	9	7	6	11	5	4	1	10	70
M chelonae	3	4	3	5	1	3	4	1	3	3	30
M. flavescens	1	–	1	1	1	–	1	–	–	1	6
Smegmatis/phlei	2	1	1	2	–	–	–	–	–	–	6
Scotochromogen–RG	–	3	4	3	2	1	7	1	–	1	22
Non-chromogen–RG	1	–	1	1	–	–	1	–	1	1	6
Others	3	2	–	–	–	–	–	–	1	–	6
Total	78	82	91	82	57	59	39	29	33	39	589

SG = Slow grower. RG = rapid grower.

chromogens showed any significant clustering in any hospital.

Discussion

The isolation of *M. tuberculosis* from urine implies that the patient has active tuberculosis requiring treatment, but it does not necessarily mean that the patient has overt involvement of the genitourinary tract. For example, approximately 25% of patients with miliary tuberculosis have a "silent" acid-fast bacteriuria (Kennedy, 1989). On the other hand, more tuberculosis patients than suspected may have renal involvement. Indeed, tuberculous interstitial nephritis leading to renal failure may be under-diagnosed and it has been suggested that notified

Table 7 Species or Groups of Environmental Mycobacteria from Hospitals at which 10 or more Strains were Isolated (based on one isolate per patient)

	Hospital															
Species or group	*1*	*2*	*3*	*7*	*14*	*18*	*28*	*29*	*33*	*37*	*40*	*52*	*59*	*61*	*62*	*68*
M. xenopi	5	23	33	–	6	4	14	1	9	3	15	5	6	7	1	1
Scotochromogen–SG	50	2	12	10	4	1	2	10	8	13	11	2	–	2	11	9
M. kansasii	5	–	8	2	1	3	2	2	2	2	2	3	–	–	1	1
MAI	2	–	1	–	–	1	–	4*	–	–	1	–	–	–	–	–
M. simiae	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–
Terrae group	–	–	–	–	–	1	–	–	–	–	–	1	–	–	–	1
M. fortuitum	–	–	2	–	–	–	–	1	3	6†	1	2	1	–	1	4‡
M. chelonae	–	–	2	–	–	4**	–	2	–	–	2	4††	3‡‡	2	–	–
M. flavescens	1	–	1	–	–	–	–	1	–	–	1	–	–	–	–	–
Smegmatis/phlei	–	–	–	–	–	1	–	1	–	–	–	–	1	–	–	–
Scotochromogen–RG	2	1	–	–	–	2	–	3	2	1	3	–	1	–	1	2
Non-chromogen–RG	–	–	1	–	–	–	–	1	–	–	–	–	–	–	–	–
Others	1	–	–	–	–	–	–	1	–	–	1	–	–	1	–	1
Total	66	26	60	12	11	18	18	27	24	25	37	18	12	12	15	19

* 1985, 1986, 1986, 1986.
† 1981, 1981, 1983, 1983, 1985, 1989.
‡ 1982, 1982, 1983, 1985.
** 1980, 1981, 1985, 1986.
†† 1980, 1981, 1982, 1983.
‡‡ 1985, 1987, 1987.
SG = Slow grower, RG = Rapid grower.

cases represent "the tip of the iceberg" (Morgan *et al.*, 1990). Reactivation of tuberculosis due to *M. bovis* frequently occurs, for unknown reasons, in the urinary system (Stoller, 1985; Yates and Grange, 1988).

The detection rate of *M. tuberculosis* and other mycobacteria in the urine depends critically on local policies for the examination of urine. Whereas at some hospitals the urine of patients suspected of having tuberculosis of any form is regularly examined for mycobacteria, at others it is examined only if renal involvement is suspected. Conversely, the relatively high number of tuberculosis patients harbouring environmental mycobacteria in their urine, 19 of 589, is probably due to the discriminate examination of urine for mycobacteria.

Environmental mycobacteria may be isolated from urine in 3 distinctly different circumstances. Firstly and most frequently, they represent a transient presence in or colonisation of the lower urethra or external genitalia. Secondly, they may be the cause of localised disease and, thirdly, involvement of the genitourinary tract may be secondary to widely disseminated mycobacterial disease.

The isolation of pigmented mycobacteria from urine, in the apparent absence of disease, was reported by Pinner (1935). In subsequent studies, chromogenic mycobacteria were also the most common type to be isolated from urine in the absence of disease. Thus Pellman and Runyon (1964) found that 34 of 42 mycobacteria isolated from the urinary tract in the USA were "Group II" (slow-growing scotochromogens), while Klotz (1970) found that 235 of 306 such isolates from Ontario, Canada, were of this type. However, strains isolated from urine in the absence of disease in Australia were non-pigmented (Carruthers and Edwards, 1965). Many textbooks state that most mycobacteria isolated from urine, or the genitourinary tract in the absence of disease, belong to the species *M. smegmatis*. As shown in this study, however, strains that could belong to this species are rarely encountered. It is probable that the name *M. smegmatis* has been used in the past to cover a range of unidentified rapidly growing mycobacteria isolated from these sources.

Being derived from the environment, it is likely that the number and nature of non-disease-associated isolations would reflect the presence of these mycobacteria in water supplies. It has been shown that some species, notably *M. xenopi* and *M. kansasii*, occur in piped water supplies in the London area and that there is a temporal variation in the numbers of these organisms in the water (McSwiggan and Collins, 1974; Collins *et al.*, 1984).

Thus the temporal variation in their isolation rate shown in this study is not surprising. The differences in the species isolated at the various hospitals probably reflect differences in the occurrence of such species in water from the surrounding areas. The organisms identified as slow-growing scotochromogens belong to the group once termed *M. aqae* or the "tap water scotochromogen". Strains bearing these names have been shown to belong to 3 species: *M. gordonae, M. scrofulaceum* and *M. flavescens* (Stanford and Grange, 1974), but since these have never been known to cause genitourinary disease we do not identify them at species level.

Clusters of isolations of a single species due to collection of urine into contaminated containers have occurred (Collins *et al.*, 1984), but no definite examples were found in this study. The few small clusters shown in Table 7 may be due to chance or environmental factors.

Localised disease of the genitourinary tract due to environmental mycobacteria is very rare. In view of the frequency of isolations of these bacteria from urine, stringent criteria for the diagnosis of disease must be adopted (Smith and Grange, 1989). Many reports provide insufficient clinical data to be certain that urinary isolates were the result of disease. Brooker and Aufderheide (1980) proposed 6 diagnostic criteria: (1) symptoms of chronic or recurrent genitourinary infection, (2) endoscopic or radiological evidence of genitourinary disease, (3) abnormal urine sediment, (4) absence of other urinary pathogens, (5) repeated isolation of the mycobacterium and (6) histological evidence of granulomatous disease and, preferably, the presence of acid-fast bacteria. They stated that the first 4 criteria should alert the physician to possible mycobacterial disease, the fifth substantially increased the probability but the sixth was essential for making a definitive diagnosis. In a retrospective study of 19 patients, none could be confirmed by these authors as having overt disease on these criteria.

The reference laboratory can help to determine the significance of an isolate by identifying it and by supplying information, from epidemiologial studies and case reports, on its likely behaviour in a given clinical situation. The final decision on its significance, however, requires more clinical information.

Several confirmed cases of renal disease caused by the "Battey bacillus", now known as *M. intracellulare*, have been reported. Two patients were treated successfully by nephrectomy (Faber *et al.*, 1965; Pergament *et al.*, 1974) and 1 by nephroureterectomy (Newman, 1970). One patient had pulmonary disease and a renal abscess due to a "Group III" (slow-growing non-chromogenic) mycobacterium, possibly also *M. intracellulare* (Tsai *et al.*, 1968).

Cases of epididymitis have been reported; 1 case in Denmark was due to *M. xenopi* (Engbaek *et al.*, 1967) and 2 in the USA were due to *M. kansasii* (Wood *et al.*, 1956; Hepper *et al.*, 1971). Lee *et al.* (1977) reported a case of chronic prostatitis with the histological appearance of mycobacterial infection and from which both *M. xenopi* and *M. fortuitum* were cultured.

In recent years, immunosuppression has emerged as a cause of disseminated infection by environmental mycobacteria, leading to the presence of these organisms in the urine. Such disseminated disease is a common occurrence in patients with AIDS and is frequently due to *M. avium-intracellulare* (Smith and Grange, 1989). Similar disseminated disease with mycobacteria in the urine, usually this species or *M. kansasii*, has been reported in pancytopenic patients (Kilbridge *et al.*, 1967; Listwan *et al.*, 1975; Thomas *et al.*, 1980), in those with congenital defects in cell mediated immunity (Thomas *et al.*, 1980) and also in a patient with no identified underlying cause (Phillips and Larkin, 1964).

Disseminated infection by the rapidly growing species *M. chelonae* and *M. fortuitum* occurs as a complication of renal failure and renal transplantation (Graybill *et al.*, 1974; Rutsky and Rostland, 1980). In one such case due to *M. chelonae*, the source of the infection was traced to a contaminated ion-exchange resin in a renal dialysis machine (Azadian *et al.*, 1981). *Mycobacterium kansasii* was isolated from the urine of a patient with pulmonary disease and chronic renal disease (Fischer *et al.*, 1968).

In conclusion, although tuberculosis is a relatively uncommon disease in South-East England, involvement of the genitourinary system is frequently encountered. While the isolation of tubercle bacilli from urine does not necessarily imply gross disease of the urinary tract, the patient certainly has active tuberculosis requiring therapy, and examination of the urinary system for strictures and other abnormalities is advisable. Isolation of environmental mycobacteria is usually of no clinical significance but overt disease of the genitourinary tract has been described and should be considered in patients with appropriate symptoms and from whom a mycobacterium has been repeatedly isolated.

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Potential Use of Tissue Adhesive in Urinary Tract Surgery

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Summary—The search for a tissue adhesive which obviates the need for suture materials in the apposition of wound edges is not new. The early adhesive products lacked the required safety and efficacy. Experimental use of a new fibrin adhesive has shown that it may have potential use where inflammatory reaction to the suture material is undesirable or water-tight sealing of the anastomosis is required.

The urinary tract provides additional problems in the use of sutures above those normally encountered in other tissues, as they will interact with both the tissues of the urinary tract and the urine within. Sutures are thus able to compromise the blood supply to a healing wound (Orr, 1969), increase the inflammatory reaction and act as a nidus for stone formation (Milroy, 1976; Morris *et al.*, 1986). These complications are common to all of the sutures in current use in varying degrees (Edlich *et al.*, 1987), depending on their individual properties. The suture materials currently available have a wide range of physical and chemical properties and vary in their strength, absorption and calculogenic potential. Tissue adhesives have subsequently been developed which aim to overcome many of these problems and should be easy to apply, effective in a wet environment and be non-toxic both locally and systemically. The early adhesive compounds, such as the cyanoacrylates, were unable to fulfil these criteria but a new adhesive, a multicomponent fibrin glue, has recently become available. This study takes a preliminary look at its potential for use in the urinary tract.

Materials and Methods

Tissue glue

"Tisseel" (Immuno AG) is a multi-component fibrin glue made from highly concentrated fibrinogen and clotting factors, which reproduce the terminal steps in the coagulation cascade. Fibrinogen in the presence of thrombin and calcium is converted to a fibrin monomer. This monomer itself then converts to a stable cross-linked fibrin polymer, which forms the adhesive bond. Aprotinin is added as a fibrinolysis inhibitor to slow the degradation of the fibrin. Preparation of the 2 components involves reconstitution of the fibrinogen in aprotinin at 37°C, and thrombin in calcium chloride and loading into a double barrelled syringe holder which allows application of equal amounts of the 2 components simultaneously. The adhesive begins to set within seconds, gaining 70% of maximal tensile strength in 10 min (Guttman, 1979). During subsequent healing the adhesive is absorbed by fibrinolysis. The adhesive action of the fibrin glue is achieved by covalent bonding between fibrin and collagen.

Method

25 male Wistar rats, weighing between 200 and 250 g, were used. Under neuroleptanalgesia a midline sagittal cystotomy was performed involving about 50% of the circumference of the bladder (1–1.5 cm). The bladder was then closed in 1 of 2 ways.

Group 1 (15 animals). The wound edges were approximated using a single 8/0 vicryl suture. The edges were then covered with a thin layer of adhesive and held together for 1 min. No bladder drainage was employed and the animals voided spontaneously upon recovery.

Based on a Poster Demonstration at the 47th Annual Meeting of the British Association of Urological Surgeons in Glasgow, June 1991

Group 2 (10 animals). The bladder edges were closed in the conventional way with a continuous, single layer of 6/0 vicryl suture. These animals acted as a control group.

The bladders were removed 3, 7, 14, 42 and 90 days after operation and examined histologically.

Results

One animal from group 1 died from a urinary leak. The remainder recovered well with no complications. At the time of removal, the bladders in both groups appeared to be of normal capacity and the cystotomy line appeared well healed. There was no evidence of significant adhesions to the wound in either group, which could have resulted from adhesive on the cystotomy line and no evidence of intraperitoneal adhesions due to extravasation of the glue around the peritoneum.

Histological examination was performed on each of the bladders removed.

Day 3. Both groups showed evidence of tissue apposition with urothelium nearly completely covering the luminal surface of the wound. There was no evidence of residual tissue adhesive on the urothelial or serosal surfaces of the cystotomy. There was an acute inflammatory reaction around the wound edges in both groups.

Days 7 and 14. The bladder edges were well adhered and low power views showed complete urothelial regeneration over the wound by 7 days (Fig. 1). Inflammatory cells were present at the wound edges with collagen being deposited across the wound. Higher power views demonstrated quite a marked reaction around the suture material in group 2 bladders (Fig. 2) with foreign body type giant cells and other chronic inflammatory cells.

Days 42 and 90. Appearances at longer intervals after surgery demonstrated complete wound healing (Fig. 3) and by 90 days the vicryl had largely been absorbed, though chronic inflammatory cells persisted around suture remnants. The wound scar appeared smaller in group 1 bladders but this was a subjective view. No smooth muscle regeneration across the cystotomy site was seen in either group and no stones or calcified material were seen.

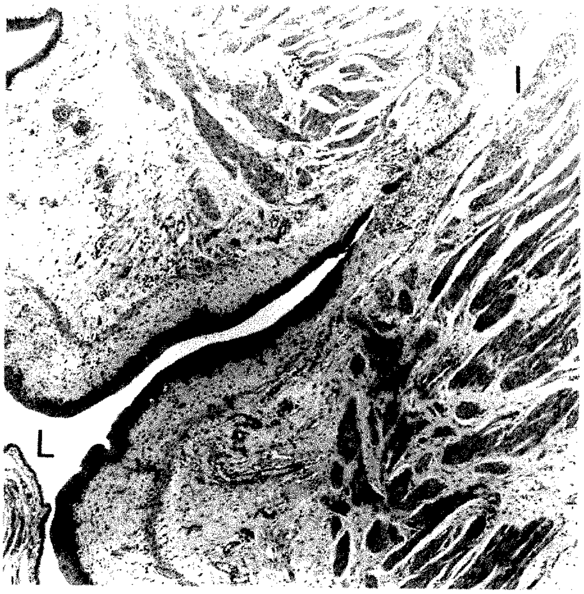

Fig. 1 Healing bladder incision in experimental animal at 7 days. L = bladder lumen. I = line of bladder incision. (H and E × 40).

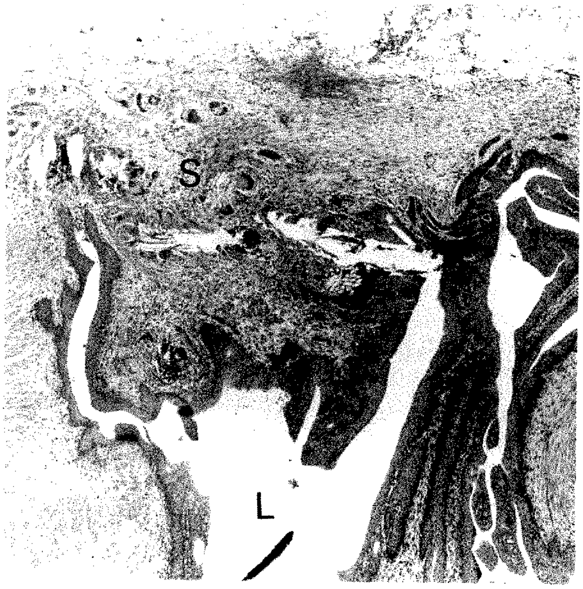

Fig. 2 Healing incision of control animal at 7 days. There is an inflammatory reaction around the suture material. S = suture material. (H and E × 40).

Discussion

The ideal suture for use in the urinary tract should maintain its strength until wound repair is complete and then undergo complete absorption without inducing an inflammatory reaction and without promoting stone formation. None of the sutures available reaches this ideal. The rate of degradation

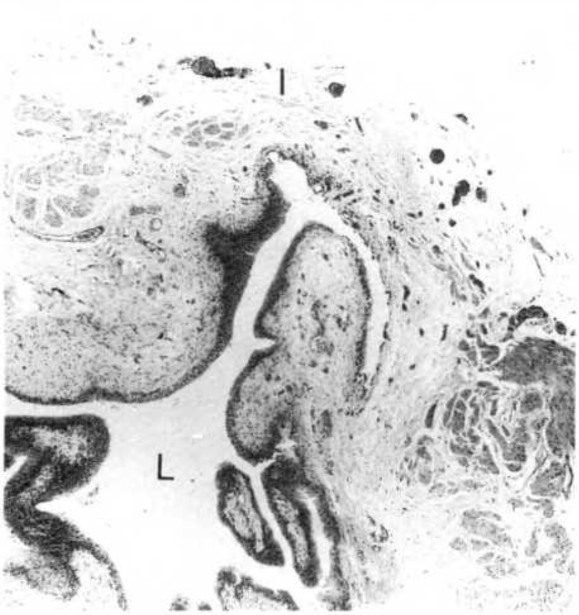

Fig. 3 Healed wound at 42 days in experimental animal. (H and E × 40).

separates sutures into 2 general classes. Those that lose their tensile strength within 60 days are considered to be absorbable and those whose strength persists are non-absorbable. Treated collagen sutures (catgut) have a variable and unpredictable strength and rate of absorption (Laufmann and Rubel, 1977) which is mediated through lysosomal enzymes, while the synthetic substitutes absorb by a non-enzymatic hydrolysis of the polymer bonds. Both cause an inflammatory reaction in surrounding tissue which is maximal with chromic catgut (Smith *et al.*, 1983; Stewart *et al.*, 1990). The incidence of urolithiasis is related to the length of time the sutures are in contact with urine and thus absorbable sutures are preferred for use in the urinary tract (Yudofsky and Scott, 1969; Kaminski *et al.*, 1978).

In most surgical situations these suture materials are adequate despite these potential complications. In some cases, however, a tissue glue has potential benefits. Many compounds have been investigated as tissue adhesives, including gelatin resorcins and cyanoacrylates, with the latter reaching clinical trials. Methyl 2-cyanoacrylate as a monomer is a clear colourless liquid which quickly polymerises on contact with water or wet tissues. This cement was studied in clinical trials for anastomosing vascular structures (Healey *et al.*, 1961; Braunwald and Awe, 1962), intestine (O'Neill *et al.*, 1962), skin and urinary tract structures (Yoho *et al.*, 1964). The cement provided a good bond strength but a number of problems were associated with its use. The heat evolved during the rapid polymerisation caused thermal injury to surrounding tissue. The polymer also showed marked histotoxicity in the longer term (Woodward *et al.*, 1964) and because of the length of time it took for absorption to occur, stones were shown to form on the surface exposed to urine (Yoho *et al.*, 1964).

The development of the fibrin adhesive has the immediate advantage that it is physiological, does not cause a foreign body reaction, has no heat of polymerisation and rapidly absorbs by fibrinolysis. The bladder has great potential for natural repair, regaining 100% of its original strength within 14 to 21 days (Edlich *et al.*, 1987), and so a rapid absorption of the adhesive should not affect wound healing. Fibrin glue has been used in a number of experimental situations including common bile duct anastomoses (Kram *et al.*, 1985), rectal anastomoses (Oka *et al.*, 1982), splenic salvage and some urinary tract procedures (Kram *et al.*, 1989). One of the potential uses is with vasectomy reversal, where it has been shown in the experimental situation that fibrin glue allows a sperm-tight anastomosis with a reduced incidence of sperm granuloma; operative time is reduced and no microsurgical skill is required (Silverstein and Mellinger, 1991). Its use in the urinary tract has not always been successful. Ureteric anastomosis with fibrin adhesive in patients undergoing stone surgery did not lead to a reduction in the leakage rate (Schultz and Christiansen, 1985) when compared with conventional sutures. These overall results are comparable to those obtained in the present study. The remarkable regenerative powers of the rat bladder, in particular the urothelium, may obscure some of the advantages of the fibrin glue as the suture material appeared to embed in the bladder tissue and rapidly became covered by urothelium. However, the fibrin adhesive appears to have a limited strength of bonding and additional transmural sutures provide tissue edge approximation and strengthen the wound repair. There is, however, a less marked inflammatory reaction in surrounding tissue and minimal potential for stone formation, even in infected urine, as the adhesive was covered by urothelium within days. An evaluation of the strength (stress and energy absorption) and elasticity of wounds repaired by various fibrin glue products was recently carried out, comparing the different formulations in terms of fibrinogen and thrombin concentrations. High concentrations of fibrinogen and thrombin have been shown to inhibit wound healing by affecting the activity of neutrophils and macrophages (Houston and Rotstein, 1988). The best formulation of the fibrin adhesives may not have been achieved yet, with optimal wound healing appearing to occur at lower concentrations of fibrinogen than are present in the adhesive products currently available (Byrne *et al.*, 1991).

There are a number of potential uses for these adhesive compounds. Tissue glue may be advantageous in reconstructive procedures involving the renal pelvis, ureter and bladder, where inflammation followed by fibrosis and urolithiasis are particularly to be avoided. Any anastomosis where a water-tight join is required may be benefited. The adhesive has the additional advantage of acting as a haemostatic agent in renal trauma or bladders damaged through radiation. The technique can also be adapted so that the adhesive is applied through the channel of an endoscope and so could be used for minor trauma of the bladder and kidney, especially where haemostasis is a particular requirement. The main advantages of this fibrin glue lie in the biological and physiological compatibility of the system and its rapid absorption, whilst the main drawback is that there is little initial inherent strength in the repair. Overall there are circumstances where urologists may find this product to be extremely useful.

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The Development of Synthetic Polymers that Resist Encrustation on Exposure to Urine

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Summary—The consequences of long-term exposure of synthetic materials to urine have prevented the development of alloplastic replacement of diseased or damaged parts of the urinary tract. Similarly, urethral and ureteric catheters require regular replacement if the complications of encrustation and blockage are to be avoided. The mechanism of encrustation is not understood completely and thus it is unclear why certain materials appear better able to resist encrustation. This study has involved the development of a new encrustation model to provide a reproducible and quantitative assessment of the susceptibility of polymers to encrustation. This model will allow beneficial characteristics of co-polymer design to be recognised, with the aim of finding new materials that are tolerant of exposure to urine. Results of co-polymers examined show that the incorporation of fluorine-containing components confers significant resistance to the formation of encrustation. It is suggested that the physico-chemical properties of polymer surfaces may be important determinants of resistance to encrustation.

The potential for the use of synthetic materials in the urinary tract is extensive. Urinary drainage devices such as urethral catheters and ureteric stents are in common use. Whilst implantable sphincteric, testicular or penile prostheses have gained acceptance, the attempts that have been made at prosthetic replacement of parts of the urinary tract have been less satisfactory. The uses that involve contact between the synthetic material and urine have all been hindered by the combined problems of the effect of urine on the material (material degradation) and the effect of the material on the urine (encrustation and stone formation). These obstacles have limited their use to temporary drainage systems such as ureteric stents and urethral catheters which can be removed or replaced with ease. Urinary tract reconstruction using alloplastic prostheses has met with limited clinical success and this is reflected in the current use of gastrointestinal tract segments for augmentation and substitution cystoplasty. However, some dissatisfaction with the long-term results of enterocystoplasty and the increased use of ureteric stents since the introduction of extracorporeal shock wave lithotripsy have highlighted the need for a material better able to tolerate prolonged exposure to urine.

The mechanism and stoichiometry of encrustation and stone formation in the presence of urease-forming organisms has been well documented both *in vivo* and *in vitro* (Griffith *et al.*, 1976). The composition and morphology of these encrustations have been demonstrated on the surface of urethral catheters (Cox *et al.*, 1987). However, it has been observed that encrustations also occur on internal stents in sterile urine and appear more likely to affect stents exposed to the urine of known stone formers (Finney, 1982; Schulze *et al.*, 1985). Previous studies of urethral catheters have shown that certain materials possess some resistance to this encrustation (Cox *et al.*, 1988) and these have subsequently been used in the manufacture of stents. The wide variety of stents available, including silicone, hydrogels, polyurethane and polyethylene, reflects the fact that there is no single material significantly superior to the others.

This study describes a new quantitative encrustation model that allows evaluation of encrustation

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resistance in polymer materials. The use of this model, combined with the ability to alter and monitor polymer composition in the bulk of the material and at the surface, allows any beneficial features to be recognised, so facilitating further polymer design.

Materials and Methods

Encrustation model

The encrustation model was developed as a system that allows the constant, controlled passage of urine over a polymer surface. The model uses human urine, as compared with the synthetic urine used in many previous models, since it was thought to be more valid physiologically and more accurately represents encrustation deposition in uninfected urine. The urine was sterilised with Urolocide [benzyl (dodecylarbamylmethyl) dimethyl ammonium chloride] at a concentration of 0.5 g/l, and sterility was confirmed by repeated urine microscopy and culture. The urine was obtained from a single source (S.A.V.H.), maintained at 37°C, and to prevent any alteration in pH or dilution of concentration, was changed every 24 h. The ionic concentration and pH were measured daily over a 14-day period to check for variability and especially for a rise in pH. The urine container was sealed to prevent water evaporation and stirred using a magnetic Teflon stirrer. Urine flowed over the polymer, driven by a peristaltic pump, and the polymer lay in a sterile sealed unit. The urine moved through single bore silicone tubing at a rate of 1.5 ml/min. Each polymer was tested continuously over a 14-day period.

Table 1 Polymer Materials Examined

Polymer	*Description*
B	Baseline homo-polymer
BF1	Lightly fluorinated co-polymer
BF2	Moderately fluorinated co-polymer
BF3	Heavily fluorinated co-polymer
S	Silicone
C	Controls

Polymers evaluated

The polymers evaluated were selected to provide a range of materials with different surface chemistries, and these are listed in Table 1. The selection contains a polymer system that can be easily manipulated to alter the chemical bulk and surface compositions of the co-polymers. The homopolymers were hydroxypropyl methacrylate (B) and hexafluoroisopropyl methacrylate. These components were co-polymerised in different ratios to produce polymeric materials with different surface chemistries. Co-polymers with the ratios of composition shown in Table 2 were produced. Silicone rubber was also examined to act as a comparison with current materials available. Control polymers were not exposed to urine at all.

The chemical composition of the polymer surfaces was examined by electron spectroscopy for chemical analysis (ESCA), since these properties may not correlate directly with the ratio of co-polymer compositions. This is because the surface region may be significantly different in structure and/or chemistry from the bulk of the polymer.

Encrustation analysis

Encrusted samples, which were approximately 24 cm^2 in size, were gently washed in distilled water to remove loose debris and then air dried. Evaluation and measurement of the encrustations that formed was by a combination of scanning electron microscopy (SEM), X-ray microanalysis and atomic emission spectroscopy (AES). The samples were analysed by AES for calcium, which represented forms of calcium phosphate deposition (brushite or apatite), and magnesium, which represented magnesium ammonium phosphate (struvite). Control polymers were examined without exposure to urine.

Results

All of the polymers examined developed some encrustations in the form of calcium or magnesium deposition, as measured by AES. Qualitative assessment of the deposits by a combination of

Table 2 Composition of Co-polymers

Polymer	*Ratio of propylmethacrylate : hexafluoroisopropyl methacrylate*
BF1	19:1
BF2	9:1
BF3	5:1

SEM and X-ray microanalysis confirmed the presence of calcium phosphate, in the form of brushite and hydroxyapatite, and magnesium ammonium phosphate as struvite. Calcium phosphate appeared over the surface of the polymer as a poorly crystalline crust. Struvite crystals were 40 to 100 μm in size and of the characteristic trapezohedral or "coffin-lid" shape.

AES revealed quantitatively the degree of calcium and magnesium deposition on each of the polymers (Figs 1 and 2). The baseline polymer consistently encrusted to a greater extent than the other polymers, though the ratio of calcium to deposition was similar in all of those tested. Incorporation of fluorine-containing co-polymers bestowed resistance to this encrustation. Furthermore, the resistance appeared related to the amount of the fluorine-containing component in the co-polymer. Using Mann–Whitney non-parametric statistics, BF2 polymers were significantly less encrusted than BF polymers (95.3% CI 52,247 $P=0.0005$). The BF3 polymer appeared less encrusted than the silicone, though statistical significance was not achieved.

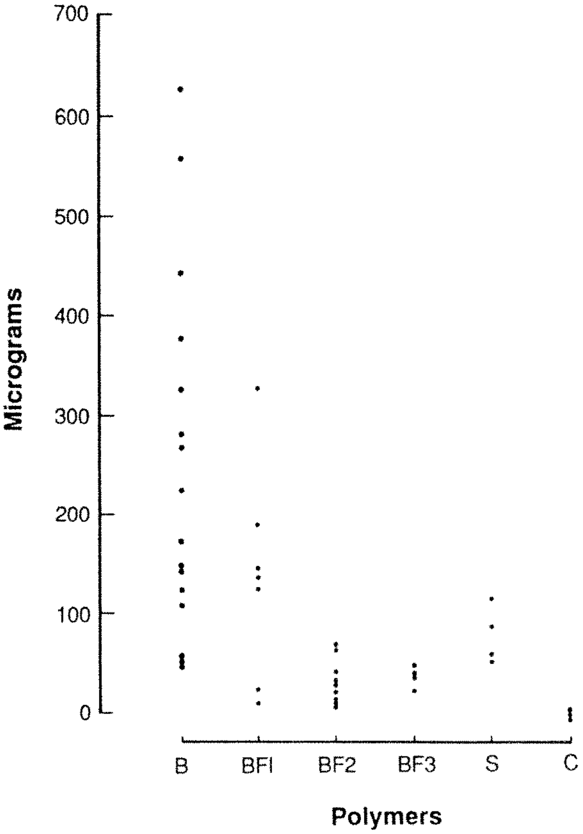

Fig. 1 The range and scatter of results of calcium deposition on the different polymers.

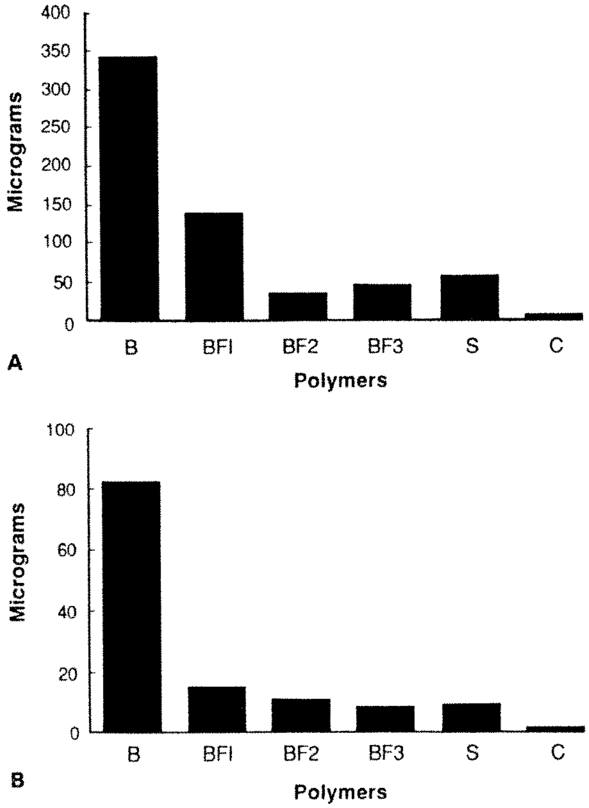

Fig. 2 (A) The deposition of calcium and (B) the deposition of magnesium on each of the polymer surfaces. The figures show the weight of the element deposited over the whole polymer.

Discussion

The formation of encrustations and stones on foreign materials placed in the bladder was recognised and documented in 1790 by Austin. Hellstrom (1938) established the distinction between sterile metabolic and infective stones and in 1950 Vermeulen *et al.* showed that encrustations on various foreign bodies in the bladder were composed of struvite. The association between this struvite and urinary infection with organisms that split urea was subsequently confirmed and the stoichiometry elucidated (Griffith *et al.*, 1976). The urealysis forms ammonium and hydroxyl ions which raise the pH of the urine and hence alter the solubility product of the urine with respect to struvite, which is precipitated. This type of encrustation forms readily on urethral catheters, leading to the persistent risk of ascending infection. The severity depends on the type of material used, the length of time in contact with the urine and the solute content of the urine. Attempts to prevent the encrustations forming by eradication of the infection or alteration of the urinary mineral composition or pH have been largely unsuccessful (Hedelin *et al.*, 1984; Griffith *et al.*, 1988).

The development of more sophisticated analytical tests has demonstrated more precisely the morphology and composition of mineral deposits on these catheters. They have shown that the deposits also contain calcium phosphate in the form of brushite or apatite, and the proportions in which they appear. In a detailed morphological study Cox and Hukins (1989) showed that *in vitro*, a layer of poorly crystalline hydroxyapatite rapidly forms on the catheter surface followed by struvite deposition. These studies were performed on urethral catheters composed of a variety of materials but have concentrated on the sequence of events that occur in the presence of infection. In sterile urine, however, studies analysing the detailed composition and morphology of these encrustations are sparse. The mechanism of formation is also not clearly understood and hence the development of materials that resist encrustation has been performed on a "trial and error" basis. The morphology of the surfaces of various urethral catheters has been examined by Cox (1990), who showed that both the material composition and the manufacturing process determined the surface roughness, as shown by SEM. The physical properties of the polymer surface in relationship to encrustation resistance have not been addressed. Previous *in vitro* models of encrustation formation have mostly been designed to look at the effect on polymers in the presence of infected urine. An example is the use of synthetic urine which enables control of urea hydrolysis to be achieved and allows direct titration of this with encrustation formation. Our model uses sterile urine flowing over the polymer surface, which is of sufficient size to facilitate quantitative mineral deposit estimation. The slow passage of urine over the polymer surface allows constant urine replacement to the polymer, without exposure to the unknown effects on encrustation formation of turbulent or high flow rates.

Many different materials have been used in the urinary tract, mostly in the form of ureteric stents but also in attempts at prosthetic replacements of parts of the urinary tract. Their limited use in upper or lower tract reconstruction is a reflection of the long-term complications of exposure to urine. One of these is demonstrated by the presence of elements used in ureteric stent manufacture found within the encrustation material, suggesting that dissolution of polymers does occur (Ramsay *et al.*, 1987). The polymers in this study have not been assessed for their solubility or toxicity to cells. This would be mandatory if further trials were to be considered, as would complete control of the polymerisation process.

We have selected a range of polymer materials to examine and, combined with the ability to alter their composition, have aimed at identifying beneficial features that will resist the tendency to encrustation. Co-polymerisation of hydroxypropyl methacrylate with hexafluoroisopropyl methacrylate has been shown to be a significantly advantageous feature, compared with the homopolymer hydroxypropyl alone. ESCA measurements show that the fluorinated groups (-CF_3 groups) are present in the hexafluoroisopropyl methacrylate component at the polymer surface. Since this is known to reduce the surface energy of the polymer, the inference is that changing the surface chemistry, and hence the surface energy, influences the encrustation process. Although further increase in the proportion of the fluorine-containing co-polymer was possible, it led to an increasingly brittle material, unsuitable for any practical use.

We have developed a new quantitive, reproducible model of encrustation formation on synthetic materials. Manipulation of polymer composition has allowed the demonstration of favourable characteristics, such as the addition of a fluorinated compound, and the model will aid in further polymer design. The model will also assist further work on identifying the mechanism of encrustation development and the possible role of factors such as infecting organisms and urinary stone inhibitors and promoters. The work has also correlated some physico-chemical properties of the polymer surface with encrustation resistance, beyond the simple morphological appearance of the surface, and work is continuing on further polymer design improvements.

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Case Reports

Inferior Vena Cava Obstruction Secondary to Urinary Retention in a Neonate

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Case Report

A 36-week-gestation male Caucasian child was born by uneventful elective Caesarian section for intra-uterine growth retardation. Birth weight was 2 kg. Shortly after birth a diagnosis of oesophageal atresia and distal tracheo-oesophageal fistula was made and the child was transferred to this hospital. Surgical repair was performed 12 h after birth.

Thirty-six hours post-operatively both legs were noted to be dusky and oedematous. A diagnosis of obstruction of the inferior vena cava (IVC) was made and ultrasound scan performed. This showed a distended bladder (100 ml) and mild to moderate bilateral hydronephrosis. After catheterisation the hydronephrosis and the changes in the legs rapidly resolved.

A repeat ultrasound scan was normal 2 days later and a subsequent micturating cystogram was also normal. There have since been no problems with micturition and the child is well at 1 year of age.

Comment

Obstruction of the IVC in the neonate is uncommon but may be due to Wilms' tumour, nephroblastoma, hepatoma or multicystic kidneys (Flye, 1983). Neonatal IVC obstruction has also been reported due to thrombosis following cannulation of the IVC for total parenteral nutrition (McLead *et al.*, 1986). There has been one reported case of an enlarged bladder causing IVC obstruction in an adult (Markus and O'Brien, 1989) but we have been unable to find any reports of this condition in a neonate.

Acknowledgement

We thank Mr J. O. N. Lawson for permission to report this case.

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Erosion of Buttress Following Bladder Neck Suspension

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Case Report

A 42-year-old female presented with a 3-month history of urinary frequency, dysuria and intermittent haematuria. She had undergone a successful endoscopic suprapubic bladder neck suspension (Stamey procedure) 4 years earlier. Initial urine analysis revealed numerous red blood cells but urine culture and cytology were negative.

An intravenous urogram showed prompt renal function with a filling defect in the left superior aspect of the bladder (Fig. 1). Subsequent cystoscopy revealed that the

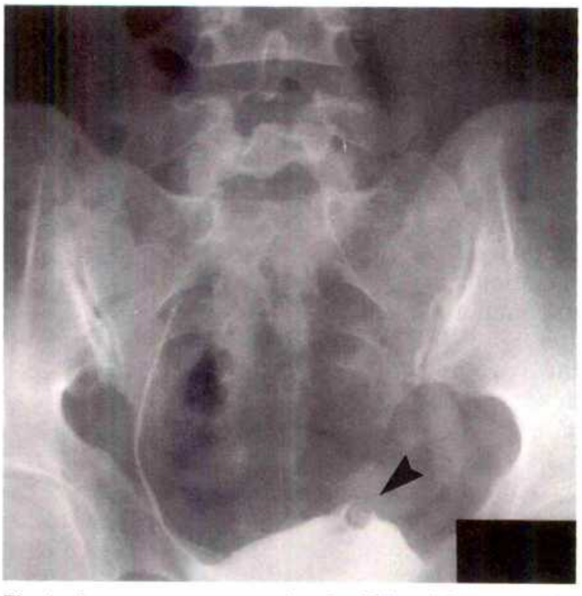

Fig. 1 Intravenous urogram showing filling defect caused by buttress (arrow).

filling defect was the Dacron buttress and nylon suture which had eroded into the bladder from the initial bladder neck suspension.

The buttress and stitch (Fig. 2) were endoscopically resected flush with the bladder mucosa. Post-operatively, the patient's frequency and dysuria resolved and she remained continent of urine.

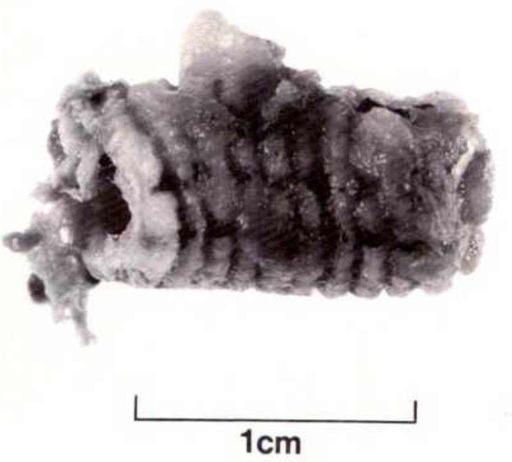

Fig. 2 Nylon suture and Dacron buttress.

Comment

The Stamey bladder neck suspension is an effective means of treating urinary stress incontinence. It has a 90% success rate which is comparable to the anterior urethropexy procedures and also decreases operating time, blood loss, hospital stay and post-operative recovery (Stamey, 1980). Complications of this procedure include post-operative urinary retention, suprapubic pain, urinary infection and inflammation around the Dacron buttress (Stamey, 1980; Richardson *et al.*, 1984). Delayed reaction to the buttress may lead to pain, induration and draining abdominal or vaginal sinuses (Guam *et al.*, 1984).

Erosion of the buttress into the lumen of the bladder is a rare complication. This is the first report of a buttress presenting as a filling in the bladder on urography. The resolution of symptoms and maintenance of continence in this patient suggest that buttress erosion can be successfully managed by endoscopic resection.

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Metastatic Carcinoma of the Prostate in Both Testes of Patients Treated with LH-RH Analogues

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Secondary tumours of the testes from prostatic carcinoma are rare and it is surprising that these tumours are now being reported more frequently. Price and Mostofi (1957) reported an incidence of 0.75% of testicular tumours due to prostatic metastases and Kirkaly *et al.* (1990) noted that about 70 such cases have been reported since the original report of Semans (1938).

We present our findings in 3 patients with metastatic carcinoma of the prostate in both testes after treatment with LH-RH analogues and discuss the possible mechanisms of spread.

All patients had histologically proven metastatic carcinoma of the prostate. Triptorelin was suggested as the treatment of choice, since they refused to accept formal or subcapsular orchiectomy. This particular drug was the only LH-RH analogue available at that time. The patients received between 9 and 13 injections of the drug at 28-day intervals.

Case Reports

Case 1 (D.M.). This patient was initially admitted with urinary retention and bone pain. Bone scan was positive for multiple metastatic disease and IVU showed prostatic enlargement. Baseline PSA was 85 ng/ml (normal 0–5). The biopsy specimen of the transurethral resection which followed was Gleason sum 8 (4+4). Refusing to have an orchiectomy, he received Triptorelin injections every 4 weeks. PSA levels dropped from 85 to 10 ng/ml. After missing an appointment (though he received his injection elsewhere), he was readmitted 10 months later with severe bone pain. PSA levels had reached 310 ng/ml. Orchiectomy was performed before any alternative treatment and histological examination showed metastatic disease in both testes, positive for PSA monoclonal staining, PAS, CEA, and negative for vimentin, A1FP and keratin (Figs 1 and 2).

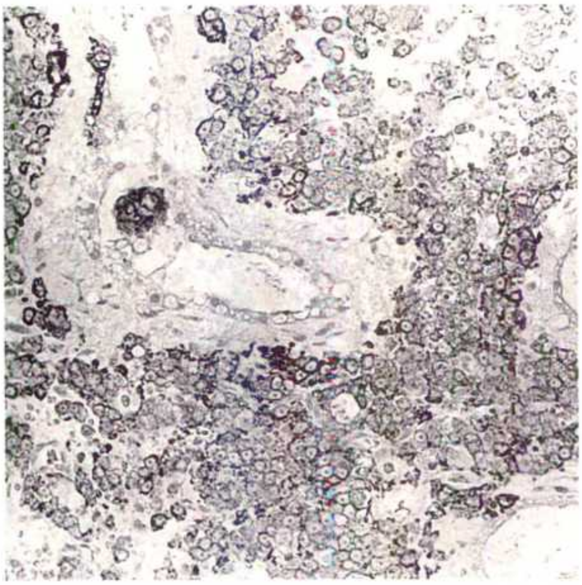

Fig. 1 Tumour cells in the interstitial tissue. Note the tumour embolus in the testicular tubules. (× 200).

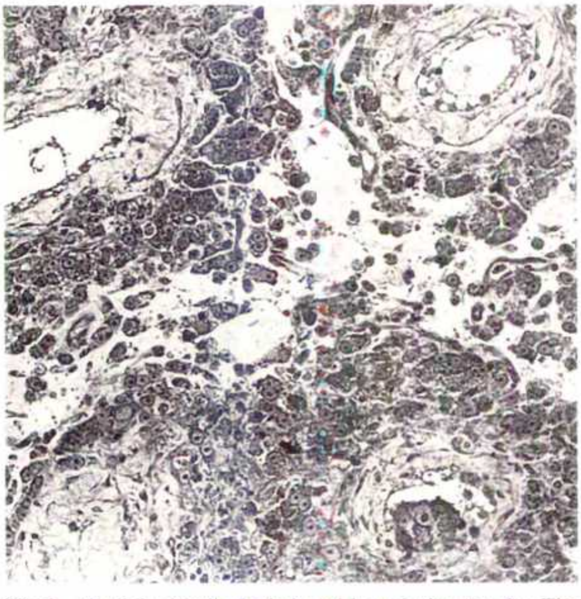

Fig. 2 Hyalinised wall of tubules with testicular atrophy. The interstitial tissue is invaded by tumour cells. Tumour embolus in the lumen of a tubule. (Masson × 200).

He is alive 14 months after orchiectomy and is being treated with 5-FU, doxorubicin and aminoglutethimide. His bone scan has improved and PSA levels are down to 15 ng/ml. Repeat biopsies of the prostate have failed to show recurrent disease within the prostate.

Case 2 (K.A.). This patient had undergone transurethral resection of the prostate (TURP) elsewhere a year before his admission. The original bone scan was positive for multiple metastatic disease and the biopsy was Gleason sum 5 (2+3). He was given Triptorelin every 4 weeks. Baseline PSA was 275 ng/ml, which swiftly dropped to 10 six months after treatment and to the normal range of 0–5 during the last 6 months. He was admitted to this department with retention of urine, neurological symptoms and bone pain. He underwent a repeat resection and the biopsy specimen was Gleason sum 9 (4+5). Bone scan showed multiple metastatic disease and PSA was 170. We performed subcapsular orchiectomy and found that both testes were infiltrated by adenocarcinoma cells positive for PSA monoclonal staining. The morphological characteristics of the metastatic disease were similar to those of the prostate (Fig. 3).

This patient died within 6 months of orchiectomy. Bone scan and PSA levels failed to improve after the operation and he developed neurological symptoms, becoming paraplegic 1 month post-operatively.

Case 3 (H.B.). This patient had been admitted to this unit 9 months earlier with retention of urine and mild bone pain. He had undergone TURP and histology showed prostatic carcinoma Gleason sum 8 (4+4). Bone scan was positive for multiple metastatic disease and baseline PSA was 70. Refusing orchiectomy, he was treated with Triptorelin and PSA was within the normal

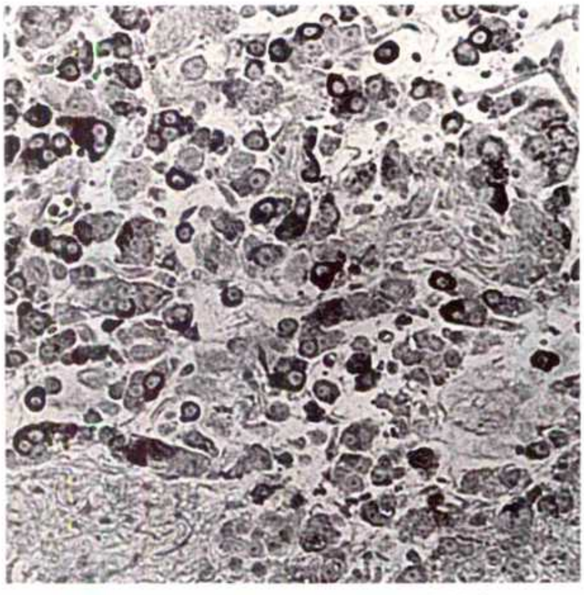

Fig. 3 PSA-positive tumour cells in the interstitial tissue.

range following the fourth injection. He was readmitted 9 months later with acute bone pain, when his PSA was 250 ng/ml. He had a repeat TURP which was followed by subcapsular orchiectomy. Histology showed the prostatic tumour to be Gleason sum 8 (4+4) and both testes were infiltrated by prostatic carcinoma (Fig. 4).

The bone scan and PSA remained at the pre-operative levels and he died from concurrent heart disease 6 months post-operatively.

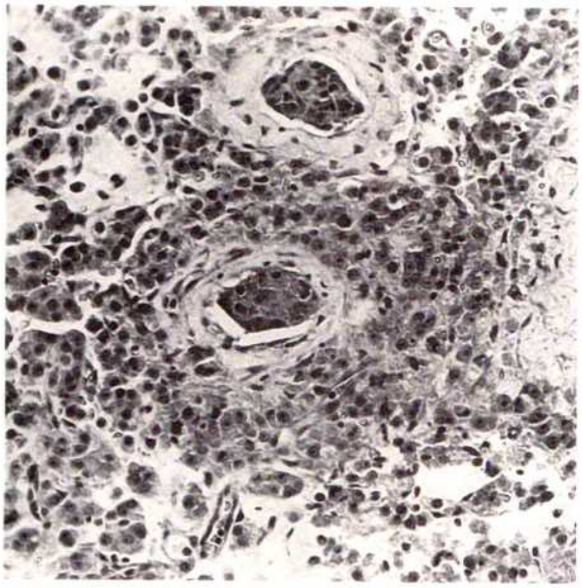

Fig. 4 Invasion of the interstitial tissue from tumour cells and 2 tumour emboli in testicular tubules. (H and E × 200).

Comment

Treatment with LH-RH analogues has become widely known among our prostate cancer patients as an alternative to orchiectomy. It is interesting that only a small percentage of Greek men with metastatic prostatic carcinoma prefer to be treated with LH-RH analogues rather than orchiectomy. We usually advise subcapsular orchiectomy and about 10% of these patients will be treated with LH-RH analogues.

It has become apparent that a few patients with prostate cancer have testicular metastases. The possible routes of spread are (1) arterial embolism, (2) retrograde venous extension or lymphatic spread, (3) direct extension, (4) through the lumen of the vas. In all cases orchiectomy was subcapsular, so that we do not know the effects on other parts of the testis. All patients presented at about the same time and all had similar therapy and symptoms. There was no clinical manifestation of the disease, which was limited to the testes. During the operation there was no indication of metastatic spread to the testes; the parenchyma was easily removed from the dura and there was no unusual bleeding.

We propose that formal orchiectomy should be performed in such cases, as intratubular tumour suggests that the route is through the lumen of the vas.

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Development of Leydig Cell Tumour in Association with Clomiphene Treatment for Oligozoospermia

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Interstitial tumours of the testis are rare, accounting for 2% of human testicular tumours. The aetiological factors are not well known. Predisposing factors such as cryptorchidism or abnormalities of hormonal regulation have been reported (Caldamone *et al.*, 1979).

We report the first case of a Leydig cell tumour associated with clomiphene treatment in an infertile man.

Case Report

In November 1987 a 45-year-old man presented with a 12-month history of infertility. He had cryptorchidism, successfully treated during childhood.

Examination revealed testes of normal size and consistency. A left varicocele was noted. Secondary sexual characteristics were normal and there was no sign of gynaecomastia.

Spermiogram analysis showed oligo-astheno-teratospermia with a concentration varying over several examinations from 7 to 18 Million/ml.

Serum hormones were normal (FSH 3.8 IU/l; LH 4.7 IU/l; testosterone 470 ng/100 ml; oestradiol 2 ng/100 ml). Intermittent treatment with clomiphene citrate 15 days/month, 50 mg/day, was then instituted for 3 months.

After the third month of treatment the patient complained of a painful swelling in the right testis. Ultrasonography showed a hypoechoic tumour 9 mm in diameter and the hormonal profile showed a marked increase in oestradiol (E2 7 ng/100 ml; FSH 2.4 IU/l; LH 3.8 IU/l; testosterone 450 ng/100 ml). After stimulation with human chorionic gonadotrophin (5000 UI/IM), the oestradiol response increased in value and in duration. These results suggested a Leydig cell tumour; the scan did not show metastasis.

In July 1988 the tumour was removed by inguinal orchiotomy and histological examination confirmed the diagnosis of a benign Leydig cell tumour.

In December 1988, 6 months post-operatively, the sperm count was 12 million/ml and the base and HCG-stimulated hormone profiles were normal. In March 1989 a varicocelectomy was performed because of persistent asthenospermia (15%), in spite of a good quality sperm count. Ten months after the varicocelectomy the patient's wife became pregnant.

Comment

Five cases of testicular tumours developing during clomiphene treatment have been reported (Reyes and Faiman, 1973; Neoptolemos *et al.*, 1981; Nilsson and Nilsson, 1985). All were malignant. This constitutes the first case of Leydig cell tumour associated with clomiphene treatment.

In this patient, clinical testicular examination and the hormone profile, including oestradiol, were normal before treatment and changed during therapy. This suggests a link between development of the tumour and treatment with clomiphene. It is, however, impossible to exclude the fact that a subclinical Leydig cell tumour could have existed before treatment, without affecting oestradiol levels.

A history of cryptorchidism found by other authors (Desmukh, 1982; Gabrilove *et al.*, 1985) supports this last hypothesis. However, there was no notable increase in spermatogenesis after ablation of the tumour, as should have been found.

The precise mechanisms through which clomiphene could be involved in the development *de novo* or the revealing of a Leydig cell tumour are not known. It is agreed that clomiphene acts on infertile men through the intermediary of an increase in FSH, LH and testosterone levels (Sorbie and Perez Marrero, 1984). This increase is not reported here because, at the time of measurement, the oestradiol secreted by the tumour exerted a negative feedback on the hypophyseal secretions. LH stimulation, normally induced by the clomiphene, acts either directly on the Leydig cell (secretion and hyperplasia) or indirectly through the intermediary of paracrine or autocrine testicular factors. Thus several mitogenic factors have been revealed in the testis such as the testicular interleukine 1-like factor whose activity is stimulated by LH and increased when there exists an alteration in the Sertoli cells or a depletion of the germinal cells (Söder *et al.*, 1989). In infertile men with oligozoospermia, such changes in the seminiferous tubules are encountered frequently, associated with Leydig cell dysfunction (Booth *et al.*, 1987; Glass and Vigersky, 1980) and sometimes with cellular hyperplasia, as observed in our series (unpublished data).

Our findings, together with those of Reyes and Faiman (1973), Neoptolemos *et al.* (1981) and Nilsson and Nilsson (1985), lead us to recommend the need for clinical surveillance, including scrotal and biological examination of infertile patients, before, during and after hormonal treatment.

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Metastatic Malignant Melanoma of the Epididymis

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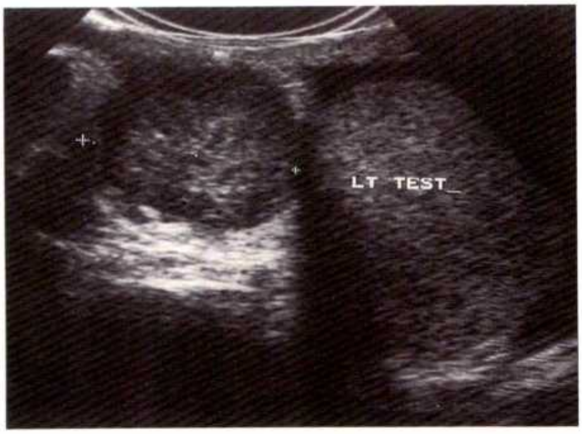
Case Report

A 38-year-old Caucasian male presented with a painless swelling of the left scrotum. Physical examination revealed a well defined uniform swelling of the head of the epididymis about 1 cm in diameter, completely separate from the testis. This was diagnosed as an epididymal cyst and the patient was reassured and discharged. He returned 6 months later because the swelling had increased in size and was tender to palpation. There were no other abnormal physical findings. The only past history of significance was a malignant melanoma of the left shoulder which had been completely excised 8 years previously. An ultrasound scan revealed a solid mass about 2 cm in diameter in the head of the epididymis with a normal testis (Fig.)



The scrotum was explored and an epididymectomy was performed.

Histology of the specimen revealed a poorly differentiated malignant melanoma. A CT scan of the chest and abdomen revealed 3 metastases in the small intestine causing sub-acute obstruction. At laparotomy the 3 segments of small intestine involved were resected. Histology again confirmed metastatic malignant melanoma. The patient later developed cerebral metastases, which are being treated by chemotherapy and radiotherapy.

Comment

Tumours of the epididymis and spermatic cord account for only 5% of all intra-scrotal tumours. About 20 to 25% are malignant but only a few are metastatic (Elsasser, 1977). A survey of the literature has revealed only 42 reported cases of metastatic paratesticular tumours, the majority of which have been included in a review by Powell *et al.* (1985). Most of them were metastatic from genitourinary or gastrointestinal primaries.

Only 5 cases of paratesticular metastatic malignant melanoma have previously been reported and 3 of these were autopsy findings in patients who had died of disseminated malignant melanomas (Anselmo *et al.*, 1979; Anderson and McGahan, 1986). One of the 2 remaining patients had widespread metastases and in the other case no details were mentioned in the report. An epididymal metastasis from a malignant melanoma in an otherwise apparently healthy patient would seem to indicate the presence of other metastases.

Acknowledgement

The author thanks Mr D. J. Farrar and Dr J. A. Banks for allowing him to report their case and Miss Tracey Wakelam for secretarial assistance.

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Hypereosinophilia, Cardiomyopathy and Transitional Cell Carcinoma of the Bladder

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Case Report

A 53-year-old lady presented with weight loss. She had a 6-year history of rheumatoid arthritis treated with

D-penicillamine. Over the preceding 18 months eosinophilia had been noted, with counts ranging between 0.9×10^9/l and 8.38×10^9/l (7–43% of total white cell count). D-penicillamine had been stopped but the eosinophilia persisted. There was no history of atopy. On examination she was cachectic. The jugular venous pressure was elevated. She had hepatomegaly and leg oedema. There were no murmurs and no cardiomegaly. Blood pressure was 105/80. Investigations revealed normal serum creatinine and albumin concentrations. Stool microscopy was negative. Bone marrow examinations showed excess eosinophils but no evidence of tumour. 2D echocardiography showed features of a restrictive cardiomyopathy. CT scanning showed bilateral hydronephrosis. Cystoscopy revealed a mass at the base of the bladder. Histology showed poorly differentiated transitional cell carcinoma. Her deterioration continued despite treatment with diuretics, steroids and palliative radiotherapy and she died.

Comment

Blood eosinophilia may indicate a variety of underlying systemic conditions. Investigation of our patient revealed no evidence of parasitic infestation, allergy, vasculitis or lymphoma. The eosinophilia was attributed to her transitional cell carcinoma of the bladder. She also had a restrictive cardiomyography probably due to endomyocardial fibrosis (Davies *et al.*, 1983), which may complicate prolonged eosinophilia of any cause. The association between blood eosinophilia and carcinoma is well recognised (Sataline and Mobley, 1967), the most frequently reported associations being with tumours of mucin-secreting epithelium, namely bronchus, gut, pancreas and uterus (Beeson, 1983). We know of no previously reported association with transitional cell carcinoma of the bladder.

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Iontophoretic Local Anaesthesia for Bladder Dilatation in the Treatment of Interstitial Cystitis

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Iontophoresis is the active transport of ions into tissues by means of an electric current: $J_i = D_i \Delta C_i / \Delta x + D_i z E C_i / kt$, where J_i is the total ionic flux, D_i the diffusion coefficient, C_i the concentration, z the valency and E the electrical field (Deister and Kasting, 1986). The first expression on the right side of the equation is Fick's Law of Diffusion, which approaches zero for bladder mucosa (Teruo *et al.*, 1986). Thus, to achieve significant ionised drug penetration into an intact bladder wall an electrical field is required, a principle that was adapted to perform isobaric overdistension of the bladder in the treatment of non-infective interstitial cystitis.

Case Report

A female multiparous patient, 38 years old, was referred with worsening symptoms of frequency, urgency, some stress incontinence, nocturia 2–4 times and micturition about 15 times daily. Urodynamic studies demonstrated a bladder capacity of 80–100 ml to painful stimulus, stress incontinence with a further 40–60 ml, elevated endovesical pressures and no vesicoureteric reflux; all urinary cultures were persistently negative and biopsy demonstrated a sub-mucosal, non-specific, inflammatory process. Diazepam and imipramine achieved no objective results, but a 3-month course of oxybutinin improved bladder capacity by about 25%. It was decided to perform bladder dilatation using an uncommon method of bladder anaesthesia, without pre-operative medication of any kind.

One hundred ml of salt-free lignocaine HCl 1% and epinephrine Cl 1/100,000 were prepared. The patient's bladder was drained and flushed with distilled water to remove residual urinary ionic "contaminants"; 80 ml of the anaesthetic solution were then infused into the bladder, at which point the patient noted the onset of discomfort/pain. An electrode of positive polarity was inserted into the catheter, a dispersive negative electrode was placed on the abdominal wall and a 15 mA DC current was applied for 10 min from a battery-powered source (equipment supplied by PHYSION srl, Mirandola, Italy). Then followed insertion of a cystoscope, visual inspection (no obvious abnormalities), a deep biopsy into the muscularis and cautery of the bleeding, all of which caused no pain or distress of any kind. The catheter and electrode were reinserted and there were successive dilatations using 50–80 ml increments of distilled water, with pauses of 3–5 min and continuing application of 15 mA current. Dexamethasone Na phosphate, 16 mg, was added to the last infusion; finally, the bladder was drained of 600 ml, 500 ml infusate and 100 ml urine, with the procedure taking about 45 min.

The level of anaesthesia was obviously satisfactory, with an inflamed bladder wall rendered insensitive to cutting, burning and stretching. The patient's pulse, blood pressure and respiration were unchanged throughout and there was full interaction between this lively, intelligent individual and the investigators. Histology of the biopsy specimen confirmed previous findings. After 6 weeks, the patient's meticulous records demonstrated urine volumes of 100–200 ml (maximum 315), nocturia once/night and micturition 5–6 times during the day, and the absence of urgency and stress incontinence.

Comment

Bladder dilatation for chronic interstitial cystitis almost always requires general anaesthesia or some form of regional block. As this report demonstrates, the urologist achieved adequate anaesthesia of the bladder wall by iontophoresis of a local anaesthetic agent and a vasoconstrictor. The investigators' choice of drugs and volumes was derived from previous studies with cadaveric bladders and some successful preliminary experience in subjects undergoing cystoscopy, biopsy and cautery. Three points are worth noting: most commercially available local anaesthetic agents of strengths 0.5–3% contain sodium chloride and these 2 ions are strong competitors for electric charge, reducing the efficiency of drug delivery; the use of lignocaine alone results in its rapid removal by an increased blood flow, with less effective anaesthesia and an increased rate of systemic absorption, whereas the addition of epinephrine eliminates these problems; dexamethasone was added to provide a post-treatment, localised, anti-inflammatory effect (Glass *et al.*, 1980).

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Metastatic Melanoma to the Testis Simulating Primary Seminoma

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Metastatic involvement of the testis is found at autopsy in 10 to 15% of patients with metastatic malignant melanoma (Patel *et al.*, 1978) but is rarely detected *ante mortem*. We present a case where the first presentation of an amelanotic type of malignant melanoma was a testicular metastasis which was initially diagnosed and treated as a seminoma. This mode of presentation has not previously been recorded.

Case Report

A 28-year-old man presented with a 5-week history of a hard irregular lesion in the right testis. At exploration a 3-cm circumscribed mass was found and a radical orchiectomy performed; histologically it was thought to be a classical seminoma. The serum alpha-fetoprotein (AFP) and beta human chorionic gonadotrophin (HCG) were normal and CT scanning showed no evident metastatic disease. After orchiectomy he was treated with 30 Gy prophylactic abdominal radiotherapy.

Eight months later hepatic and para-aortic node metastases developed and he was referred for chemotherapy. At this time a 3-cm subcutaneous mass above the right knee was noted which had been present for at least 1 year and had increased in size. This was excised.

There was a mixed response, with regression in some metastases but progression in others following cisplatin and etoposide chemotherapy. On change of chemotherapy to decarbazine, vindesine and CCNU, substantial shrinkage of metastases occurred but cytologically proven meningeal disease later developed and he died 14 months after the orchiectomy. An autopsy was not performed.

Pathology

Examination of the testis showed a well circumscribed mass 3 × 3 × 2.5 cm which was lobulated and consisted of multiple fleshy nodules. Similar nodules up to 0.2 cm in diameter were present separate from the main mass. The tumour (Fig. 1A) consisted of nests of large polygonal cells with vacuolated or eosinophilic cytoplasm and a large nucleus containing a prominent eosinophilic nucleolus. Smaller nodules of tumour cells were present throughout the testis. There was no lymphocytic infiltrate. The lesion above the knee (Fig. 1B) was a firm white mass 2.7 × 1.7 × 1.5 cm lying in the deep dermis and subcutaneous tissue. The overlying epidermis was normal. The histological appearance of the tumour cells was similar to the testis. Mitoses were frequent. Special stains failed to reveal mucin, but melanin pigment was identified in macrophages and occasional tumour cells. Immunocytochemistry of both tumours was identical. The tumour cells showed diffuse strong cytoplasmic staining for S-100 protein and vimentin (Fig. 2). There was faint positivity with antibody to neurone specific enolase

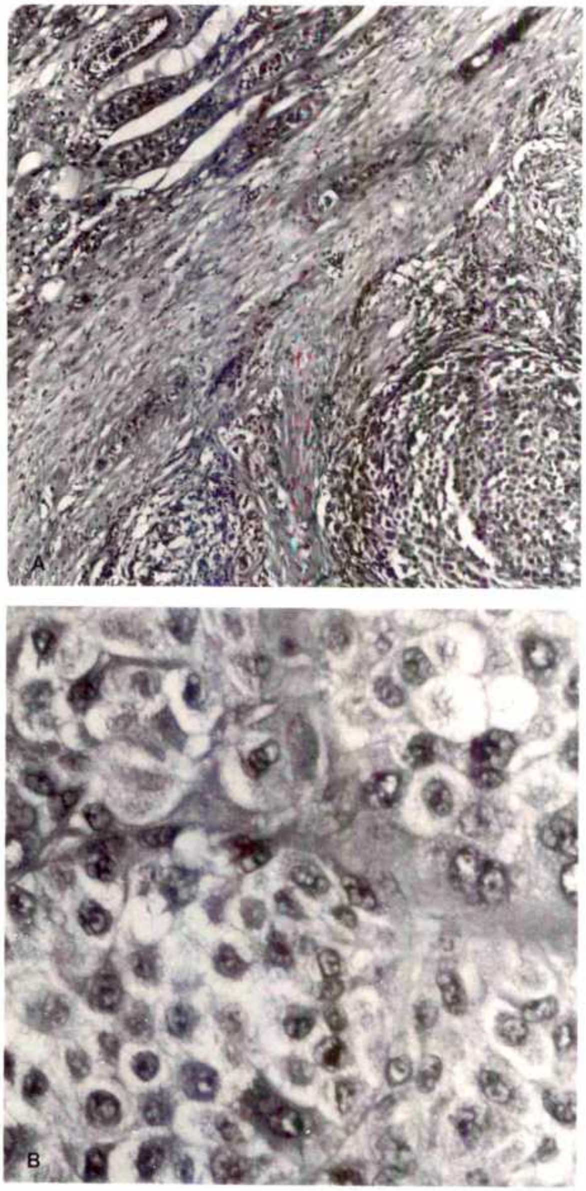

Fig. 1 (A) Testicular metastasis. (B) Primary tumour. Both show large polygonal cells with a large nucleus. (H and E × 540).

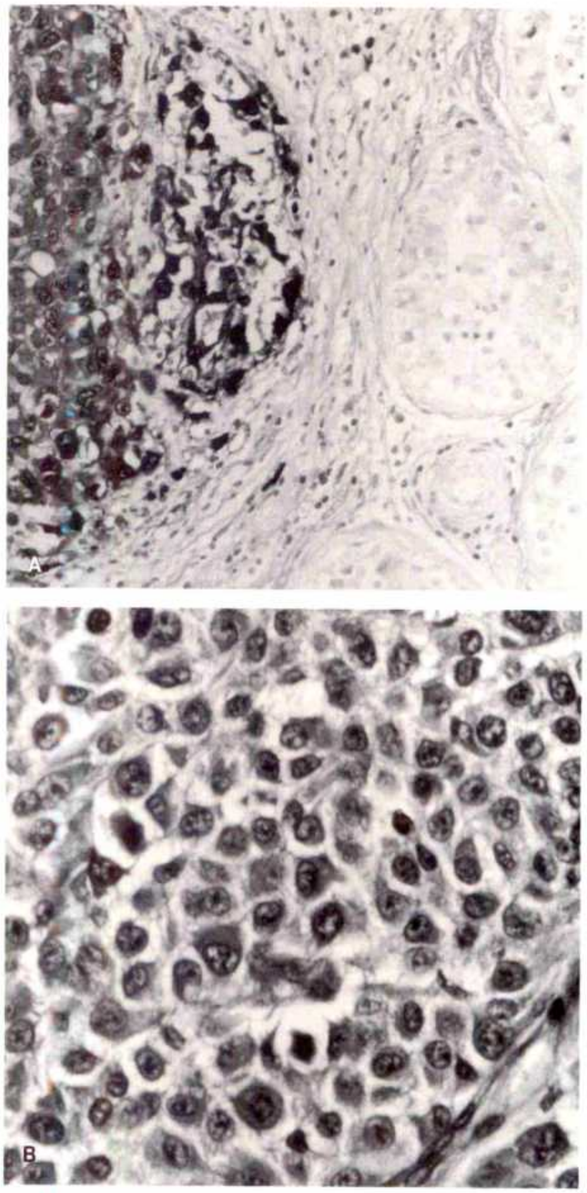

Fig. 2 (A) Testicular metastasis. (B) Primary tumour. Tumour cells stained with antibody to S-100 protein showing cytoplasmic positivity (× 216).

but no staining with antibodies to cytokeratin, carcinoembryonic antigen, epithelial membrane antigen, AFP, beta-HCG or placental alkaline phosphatase.

Comment

This patient was initially thought to have a testicular seminoma and the histological appearance of the testicular mass was not incompatible, although the absence of lymphocytic infiltrate and the failure to respond substantially to cisplatin-based chemotherapy were most unusual. However, the immunocytochemistry results, with positive staining to S-100 and vimentin and negative to placental alkaline phosphatase, were highly suggestive of metastatic melanoma. The lesion above the right knee predated the appearance of the testicular mass, indicating that this was the likely primary tumour, although it is possible that it was also a metastasis from an undiscovered primary elsewhere. As this lesion did not involve the epidermis it probably represented a malignant melanoma of soft parts. This is an uncommon malignancy originally described as a sarcoma of tendons and aponeuroses, but it is now known to be of melanocytic origin (Chung and Enzinger, 1983) and the area around the knee is one of the most common sites for it to arise (Sara *et al.*, 1990). Metastatic tumour to the testis is very rarely the presenting manifestation of a solid tumour. In a review of 127 patients with testicular metastases, 12 with melanoma were identified (Haupt *et al.*, 1984) but in none was this the initial presentation. This is the first reported case where this has occurred.

Acknowledgement

We thank Mr J. G. W. Feggetter, Department of Surgery, Ashington General Hospital, for help in reporting this case.

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Requests for reprints to. B. M. J. Cantwell, University Department of Clinical Oncology, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE.

British Journal of Urology (1992), **69**, 666

Point of Technique

Diagnosis of Urinary Leak in a Critically Ill Patient Using Bedside ^{99m}Tc-DTPA Renal Scanning

H. D. M. SPAPEN, A. JACOBS, J. BRAECKMAN and L. P. HUYGHENS, *Critical Care Department and Departments of Nuclear Medicine and Urology, Vrije University, Brussels, Belgium*

Most information on the use of renal scintigraphy in the intensive care unit comes from experience with renal transplant patients. The technique is non-invasive and can reliably detect ureteric obstruction, extravasation of urine and the absence of renal perfusion (Alavi *et al.*, 1990).

Case Report

A 42-year-old woman underwent palliative abdominal and retroperitoneal surgery for carcinoma of the cervix. Bilateral ureteric stents were placed per-operatively since both ureters had to be dissected free from surrounding tumour tissue. Post-operatively the patient remained anuric. Sonography showed bilateral hydronephrosis grade III. Retrograde urography showed a right-sided urinary leak (Fig. 1). Withdrawal of the ureteric stents induced diuresis.

The patient developed acute respiratory insufficiency that required mechanical ventilation. Urinary output fell again over the following days despite normal haemodynamic status, the absence of nephrotoxic drugs and normal aspect of the kidneys on repeated ultrasound. Bedside ^{99m}Tc-DTPA renal scintigraphy revealed migration of tracer activity beyond the upper pole of the right kidney (Fig. 2), corresponding to the urinary leak. After 3 days the patient began to urinate spontaneously. Retrograde urography and renal scintigraphy were repeated but failed to visualise any leakage, which suggested spontaneous closure of the defect.

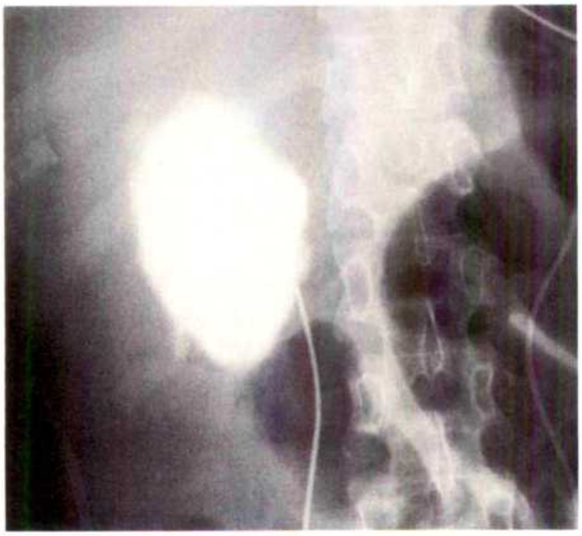

Fig. 1 Retrograde urography showing a right-sided urine leak.

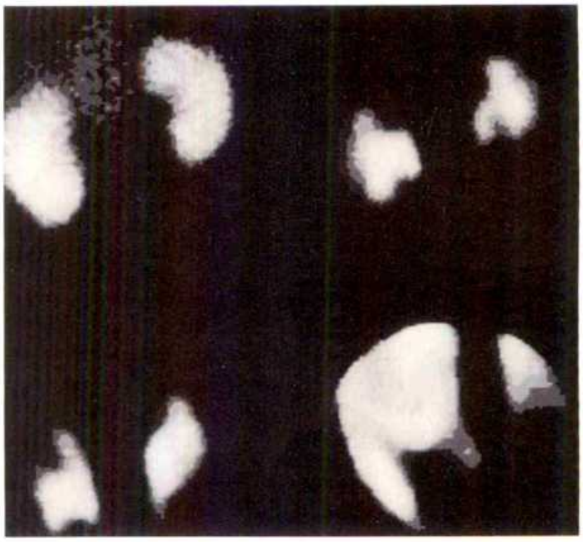

Fig. 2 Successive anterior images of ^{99m}Tc-DTPA renal scintigraphy at 4 min (upper left), 12 min (upper right), 20 min (lower left) post-injection and after administration of frusemide (lower right). The lower images show progressive migration of tracer activity in the upper pole of the right kidney, followed by accumulation of tracer in the right lateral pararenal region.

Comment

The vascular supply of the ureter is easily damaged, with ureteric ischaemia leading to obstruction or leakage. Several factors may have accounted for the ureteric leak in our patient: previous pelvic irradiation with harmful effects on the ureteric anatomy, per-operative ureteric dissection with resulting oedema and right ureteric perforation.

Bedside renal scintigraphy can provide a rapid and accurate diagnosis of ureteric leakage in severely ill patients in whom clinical examination, renal ultrasound and urography are inconclusive or equivocal.

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Alavi, A., Grossman, R. and Siegal, A. (1990). Intraperitoneal urine leak following renal transplant: the role of radionuclide imaging. *J. Nucl. Med.*, **31**, 1206–1210.

Requests for reprints to: H. D. M. Spapen, Critical Care Department, Vrije Universiteit Brussel, 101 Laarbeeklaan, B-1090 Brussels, Belgium.

British Journal of Urology (1992), 69, 667–669

Correspondence

Dear Sir,

re **The persistent indwelling catheter.** S. K. Iyer. *Br. J. Urol.*, **69**, 100, 1992.

I read with interest the introductory part of this article listing the possible methods of deflating a blocked balloon. I use a simple atraumatic method of deflation. This involves passing the long stylet that comes with an ordinary round-tipped 5F ureteric catheter well lubricated with lignocaine up the side channel into the balloon. I have done this several times and so far have always been successful. As soon as the obstruction (usually at the proximal end) is overcome, there is a sudden gush of water. The balloon remains intact and can easily be checked by inflation. Antibiotics are not necessary, the use of a hospital bed is avoided, and the radiologist's time is saved. There is also no need for further investigations to exclude pieces of the balloon in the bladder.

Yours faithfully,

V. Radhakrishnan
Department of Urology, Royal Infirmary, Sunderland.

Dear Sir,

re **Gastrocystoplasty in children.** Evelyn H. Dykes and P. G. Ransley. *Br. J. Urol.*, **69**, 91–95, 1992.

Dykes and Ransley have reported a fascinating series of gastrocystoplasties and highlighted the potential problems of excess acid secretion in these children. The size of the gastric pouch would appear to be of prime importance in avoiding excess acid secretion. This would be expected from the observations in duodenal ulcer disease where patients with duodenal ulcers excrete more acid over a 24-h period (Henning and Norpoth. *Dtsch. Arch. Klin. Med.*, **172**, 558, 1932) and the probably relationship to increased parietal cell mass in these patients. Unlike the stomach, where food can buffer gastric acidity, the role of buffers within the urine is unclear. It is also relevant that while there were seemingly only small changes in pH in their patients, this of course is reflected in large changes in hydrogen ion concentration (due to the inverse log). These might be expected to have a more detrimental effect on the bladder mucosa as it does not have the intricate defence mechanisms against acid secretion that the gastric mucosa does. However, as they have shown, treatment with traditional anti-ulcer medication is effective.

Yours faithfully,

S. Chiverton
Department of Urology, St Mary's Hospital, Portsmouth.

Dear Sir,

re **An appliance to direct urine flow following penile amputation.** C. L. Garbutt *et al. Br. J. Urol.*, **68**, 328–329, 1991.

The authors are to be commended for creating this simple appliance. However, due credit for this original thought should be given to A. L. Manson (*J. Urol.*, **141**, 895, 1989).

Yours faithfully,

K. S. Swami
Department of Urology, Southmead Hospital, Bristol.

Dear Sir,

re **Partial extraction of Double-J stent during nephrostomy tube removal and its prevention.** S. Gepi-Attee *et al. Br. J. Urol.*, **68**, 552–553, 1991.

We read this case report with interest. The authors have suggested that the nephrostomy tube be removed before completing the procedure of Double-J (DJ) stenting under the same anaesthetic. There are, however, situations where one might wish to retain the nephrostomy tube longer, as for bleeding during the procedure, removal of an infective calculus or percutaneous access needed for chemolysis. We have come across such situations and have found the following manoeuvres useful in preventing inadvertent DJ extraction through the percutaneous tract with the nephrostomy tube:

1. In the case of a Malecot catheter nephrostomy, a flexible stylet is passed in to straighten its flanges. The Malecot catheter is then rotated on its longitudinal axis for 2 or 3 turns clockwise and then anticlockwise. If the DJ stent has been grasped between the flanges, there is increasing resistance to the rotatory motion. The stylet is then withdrawn and the rotating manoeuvre is repeated with open flanges. The stylet is passed again, disengagement is confirmed by free rotation and the nephrostomy tube is safely removed. The entire procedure is performed under fluoroscopic control.
2. In the case of a pigtail nephrostomy tube, a guide wire of appropriate size is passed through the tube in order to straighten the coil. The tube can then be pulled out without risk of extrusion of the DJ stent, since inadvertent removal of the stent with a pigtail nephrostomy tube occurs only when the coils of the 2 tubes become intertwined. The procedure may or may not be performed under fluoroscopic control.

In the event of partial extrusion of the DJ stent through the nephrostomy tract, we have been able to reposition the same stent over a guide wire which is passed through the lumen of the stent and guided into the bladder. Care must be taken not to leave the proximal end of the stent in the nephrostomy tract and it should be pushed and coiled well into the pelvicaliceal system.

Yours faithfully,

D. Dalela and R. Ahlawat
Department of Urology, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, India.

Dear Sir,

re **Gluteal device for penile injection**. A. M. Helmy. *Br. J. Urol.*, **68**, 400–403, 1991.

When we read the "original" article by Dr Helmy we justifiably felt a sense of déjà vu, as we had already described the very same system (K. M. Desai *et al.*, *Br. J. Urol.*, **60**, 267–270, 1987), although we now understand that Dr Helmy's original manuscript was submitted to the journal before publication of our article. The only difference is the siting of the device by Helmy in the gluteal region, whereas we implanted our drug release system more conveniently in the anterior abdominal wall. We were careful to conclude from our experience that the concept was feasible but that there was concern about the long-term patency and durability of the delivery system.

The report by Helmy gives no indication regarding the length of follow-up of his patients. As it is clear that several years have elapsed since the original submission of the manuscript and its publication, may we ask Dr Helmy to comment on his long-term results?

Of even greater concern is the statement that some of his patients were having normal erections without the need for injections—this seriously questions his patient selection criteria.

Yours faithfully,

J. G. Gingell, K.M. Desai and T. J. Floyd
Department of Urology, Southmead Hospital, Bristol.

Reply from Dr Helmy. In reply to Mr Gingell and colleagues I wish to explain that in spite of the similarity of the idea described in our respective articles, the implantable device is different and I am using a special device of my own invention which is manufactured to suit the application. Having considered placing it in the abdominal wall, we chose the gluteal site because the iliac bone provides the counter pressure required for injection; the gluteal region is the most popular site for injection and fixation in this position is more stable.

Concerning the long-term patency and durability of the device, there have been no problems and 200 patients have now been operated upon.

Mr Gingell and colleagues have questioned my selection criteria. As explained in my article, however, the device is suitable for a wide variety of patients with erectile problems, some of whom may still be able to achieve some spontaneous but inadequate erectile activity.

These include patients with psychological problems, paraplegic, pelvic exenteration, diabetic, severe premature ejaculation and patients receiving erection-inhibiting drugs.

Dear Sir,

re **Determination of pre-orchiectomy serum levels of alpha-fetoprotein and human choriogonadotrophin in testicular cancer.** Sophie D. Fosså and M. Mason. *Br. J. Urol.*, **69**, 108, 1992.

Drs Fosså and Mason wring their hands over the feckless ways of British and Norwegian urologists: only 41% of patients referred to oncologists with testicular cancer had had serum AFP and HCG performed prior to orchiectomy. Their concern is that in the case of a histological diagnosis of a stage I seminoma a raised AFP pre-operatively may have normalised post-operatively and the patient may erroneously receive abdominal radiotherapy rather than other treatments. They admit that this occurrence is extremely rare.

In the hierarchy of urological malfeasance this must rate very low. Abdominal irradiation controls the retroperitoneum well in stage I non-seminomatous testicular cancer (Roth *et al. Int. J. Androl.*, **10**, 255–262, 1987), and of 13 stage I AFP-producing seminoma patients treated in this way (reviewed by Oliver, R. T. D. (1991). In *Testicular Cancer*, ed. Horwich, A. London: Chapman and Hall) only one subsequently relapsed. There is a concern that in the event of chemotherapy subsequently being required, prior abdominal irradiation may significantly reduce the patient's tolerance. But is the eventuality more than hypothetical in this case?

I accept that serum tumour markers can assist in the diagnosis of a difficult testicular swelling and that the knowledge of plasma levels in the peri-operative period can—when they fail to fall—allow the diagnosis of metastatic disease to be made a few days earlier than otherwise. Patients occasionally come to harm where there is a delay in referral for oncological assessment, but I challenge Drs Fosså and Mason to produce patients who have been harmed by the lack of a pre-operative tumour marker estimation.

Yours faithfully,

S. J. Harland
Institute of Urology and Nephrology, Middlesex Hospital, London.

Reply from Dr Fosså. In the oncological community it has always been "good clinical practice" to attempt to make the correct diagnosis of a malignancy at the time of first presentation in order to give optimal treatment in the first place. In his letter Dr Harland actually challenges this philosophy for patients with germ cell tumours. Is it his opinion that all stage I patients can be given abdominal radiotherapy, since those who will relapse (most probably those who have non-seminoma) can subsequently be given effective salvage chemotherapy?

In our opinion it is of considerable clinical interest to distinguish seminoma patients from those with non-seminoma and the "real" seminoma patients from those with an AFP-producing seminoma, even though pre-orchiectomy AFP levels will assist this discrimination in only a small minority of the seminoma patients with stage I tumours. By knowing the pre-operative AFP levels some treatment-induced risks can be avoided in patients with AFP-producing seminoma:

(1) *Combined radio/chemotherapy.* The combination of radiotherapy plus cisplatin-based chemotherapy leads to increased somatic long-term morbidity (renal, gastrointestinal, urological) if compared with chemotherapy alone. Combined radio/chemotherapy may even be more carcinogenic than either of these treatments given alone.

(2) *Psychological distress.* Testicular cancer patients who develop an unexpected relapse seem to have more long-term psychological problems than those who are cured by the primary treatment.

(3) *Waste of health care resources.* Geographic factors mean that testicular cancer patients undergoing radiotherapy sometimes require 3 weeks' hospitalisation. This can be justified only if radiotherapy is medically indicated.

(4) *Intensity of follow-up.* At least in Norway, irradiated seminoma patients follow a schedule which is less intensive than that designed for non-seminoma patients, based on medical aspects and health care economics.

The following aspects should also be considered:

(1) Some co-operative groups base their treatment schedule for non-seminoma stage I patients on the knowledge of their pre-operative AFP levels.

(2) Knowing that an individual patient had an elevated AFP before orchiectomy, the pathologist (even if less experienced in the diagnosis of testicular tumours) will perform histochemical staining of the specimens even though the evidence of yolk sac elements is lacking at the first view.

In conclusion, there is no doubt that knowledge of pre-orchiectomy AFP levels facilitates the correct diagnosis in testicular cancer patients. This knowledge helps to determine the correct primary treatment for the individual patient, thus minimising toxicity and expense.

British Journal of Urology (1992), 69, 670

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth. 21–26 June 1992

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £1000 to the author of the article(s) judged to be the most outstanding each year (2 volumes) in the British Journal of Urology. Candidates for the prize must be Fellows of the Royal College of Surgeons in the British Isles, Canada, Australia or South Africa; they must be undergoing urological training or have obtained a consultant post not more than 10 years before the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prizewinner must submit a programme of visits to urological centres outside Britain. This prize is not necessarily awarded annually.

Scholarships for Experimental and Clinical Research in Urology

The European Association of Urology and the European Board of Urology will award three scholarships for research in Urology. Each scholarship will be awarded for one year, starting on 1 July 1992, at a maximum of 33,000 ECU at any appropriate institution in the world. Further information from: The European Board of Urology Education Committee, P.O. Box 25285, 3001 HG Rotterdam, The Netherlands. Tel: 31.10.436.6665. FAX: 31.10.436.6669.

Shackman Travelling Fellowship 1993

Applications are invited from Medical Practitioners registered in the United Kingdom who are either trainees in Urology or Organ Transplantation or Consultant Urological Surgeons or Consultant Surgeons with a major commitment to transplantation of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for application is 1 September 1992.

Further particulars and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB2 9AG.

British Journal of Urology (1992), 69, 671–672

Diary

1992

July 5–12	ALASKA '92—CRUISE THE INLAND PASSAGE—Breast Imaging at Sea. Contact: ALASKA 92—Breast Imaging at Sea, Medical Seminars International, Inc., 18981 Ventura Blvd, Suite 303, Tarzana, CA 91356, USA.
July 12–19	ALASKA '92—CRUISE THE INLAND PASSAGE—Magnetic Resonance Imaging-Musculoskeletal Imaging at Sea. Contact: ALASKA 92—Magnetic Resonance Imaging at Sea, Medical Seminars International, Inc., 18981 Ventura Blvd., Suite 303, Tarzana, CA 91356, USA.
July 22–25	European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
August 2–5	International Society for Dynamics of the Upper Tract. Ninth Meeting. Akita, Japan. Contact: Dr B. L. R. A. Coolsaet, Klina Hospitals, Campus St Jozefziekenhuis, 2950 Kapellen, Antwerp, Belgium.
August 7–9	Ninth Meeting of International Society for Dynamics of the Upper Urinary Tract. Akita, Japan. Contact: Dr Seigi Tsuchida, Department of Urology, Akita University School of Medicine, 1-1-1 Hondo, Akita, 010 Japan. FAX 81-188-36-2619.
August 24–27	Edinburgh Urological Festival. Edinburgh. Contact: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.
August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
August 24–27	VIIth International Symposium on Urolithiasis and Related Clinical Research. Cairns, Australia. Contact: Dr Rosemary L. Ryall, Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia 5042.
August 30–September 4	Ninth Congress of the International Pediatric Nephrology Association. Pediatric Urology Section. Jerusalem, Israel. Contact: Dr Amicur Farkas, Department of Urology, Shaare Zedek Medical Center, P.O.B. 3235, Jerusalem 91031, Israel.
August 31	Workshop in Sacral Anterior Root Stimulation in Spinal Cord Injured Patients. Halifax, Nova Scotia, Canada. Satellite meeting of International Continence Society, September 1–4. Contact: Professor E. P. Arnold, Department of Urology, Christchurch Hospital, Christchurch, New Zealand.
September 3–6	Tenth World Congress on Endourology and ESWL, Singapore. Contact: Secretariat, c/o Department of Urology, Singapore General Hospital, Outram Road, Singapore 0511.
September 14–18	Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.

September 15–18	Euro-American Conference on Urological Cancer—Clinical and Biological Progress. Athens, Greece. Contact: Erasmus Conference Centre, International Congress Organizers, 227—229 Kifissias Avenue, Athens 145 62, Greece.
September 17–18	Seventh Annual Paediatric Urology Course Selwyn College, Cambridge. Contact: Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
September 21–23	VIII Andrology Course. Barcelona, Spain. Contact: Secretaría General, Fundación Puigvert, c/. Cartagena 340–350, 08025 Barcelona, Spain. Tel: 34.3 2355614. Fax: 34.3 4559938.
September 23–25	Polish Association of Urology Annual Meeting. Wroclaw, Poland. Contact: Organizing Committee, Katedra i Klinika Urologii, 50–043 Wroclaw, Pl. 1-Maja 8, Poland. Tel: 347-59. Fax: 254 101.
October 1–3	Annual Meeting of the Swiss Society of Urology. Leysin, Switzerland. Contact: Prof. Dr P. Graber, Clinique de Chirurgie Urologique, Hôpital cantonal, CH-1211 Genève 4, or Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich.
October 1–3	Fourth World Congress of VideoUrology. Monte Carlo, Monaco. Contact: Convergences—VideoUrology '92, 120 Avenue Gambetta, 75020 Paris, France. Telex: 216 911 F. Fax: (33-1) 40 31 01 65.
October 7–11	1992 Duke Urologic Assembly. "Contemporary Issues in Urology". Pinehurst, North Carolina. Contact: Linda Mace, Assembly Coordinator, Box 3707, Duke
October 9–10	BAUS Autumn Meeting, Swansea. Contact BAUS Office.
November 1–4	Third International Workshop on Carcinoma *in situ* and Cancer of the Testis. Copenhagen, Denmark. Contact: Workshop Secretariat, c/o Professor N. E. Skakkebaek, University Department of Growth and Reproduction, Section 5064, Rigshospitalet, 9 Blegdamsvej, DK-2100, Copenhagen, Denmark.
November 8–10	Fourth International Conference of the Society for Minimally Invasive Therapy. Dublin, Ireland. Contact: Professor J. Fitzpatrick, 47 Eccles Street, Dublin 2, Ireland. Tel: +353-1-308530. Fax: +353-1-300345.
November 27–28	International Postgraduate Course on Reconstructive Surgery of the Lower Urinary Tract in Children. Amsterdam, The Netherlands. Contact: Conference Secretariat, Bureau PAOG Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands: Tel: +31 20-566 4801. Fax: +31 20-696 3223.
December 4–5	Eighth International Steglitz Paediatric Surgical Congress. Berlin, Germany. Contact: Dr F. Schier, Kinderchirurgie, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (030) 798 4181 or 798 2909; Fax: (030) 798 4141.

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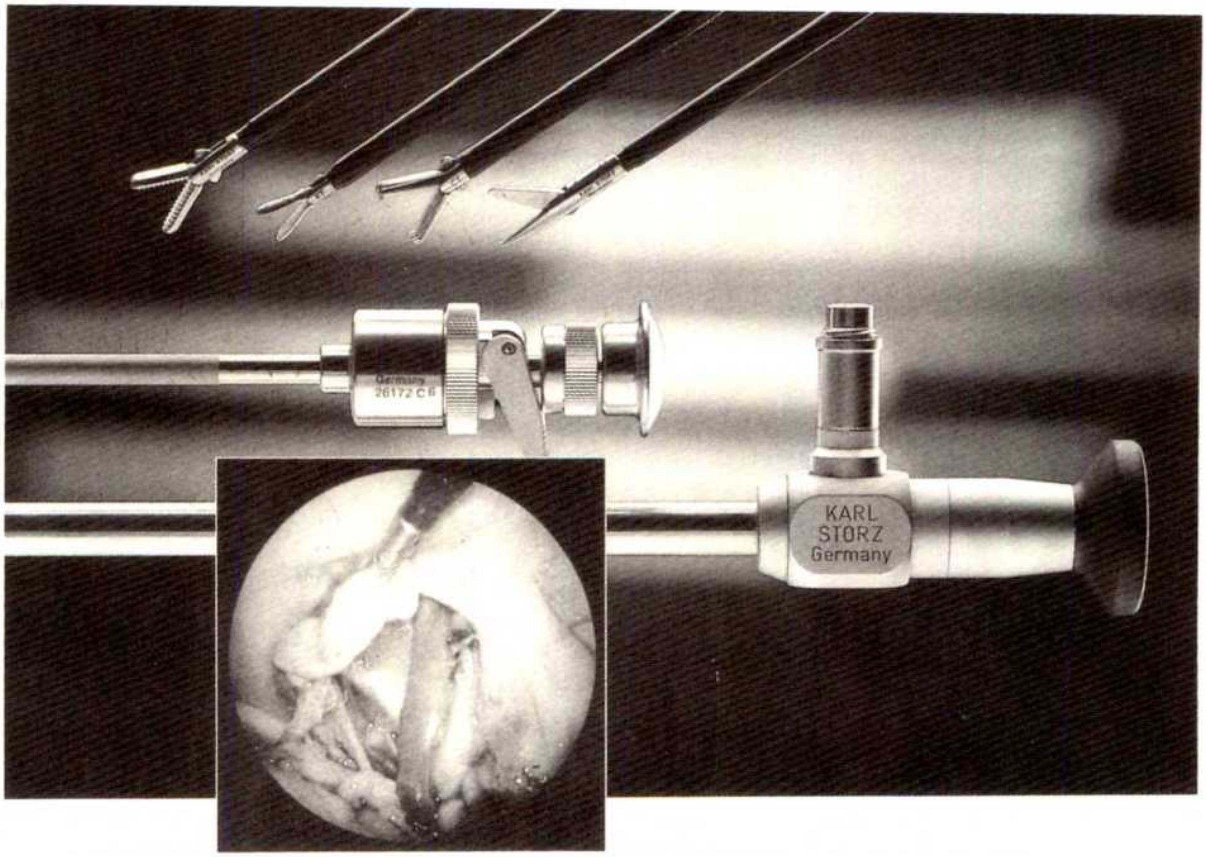
Minimally invasive Surgery
Laparoscopic Lymphadenectomy



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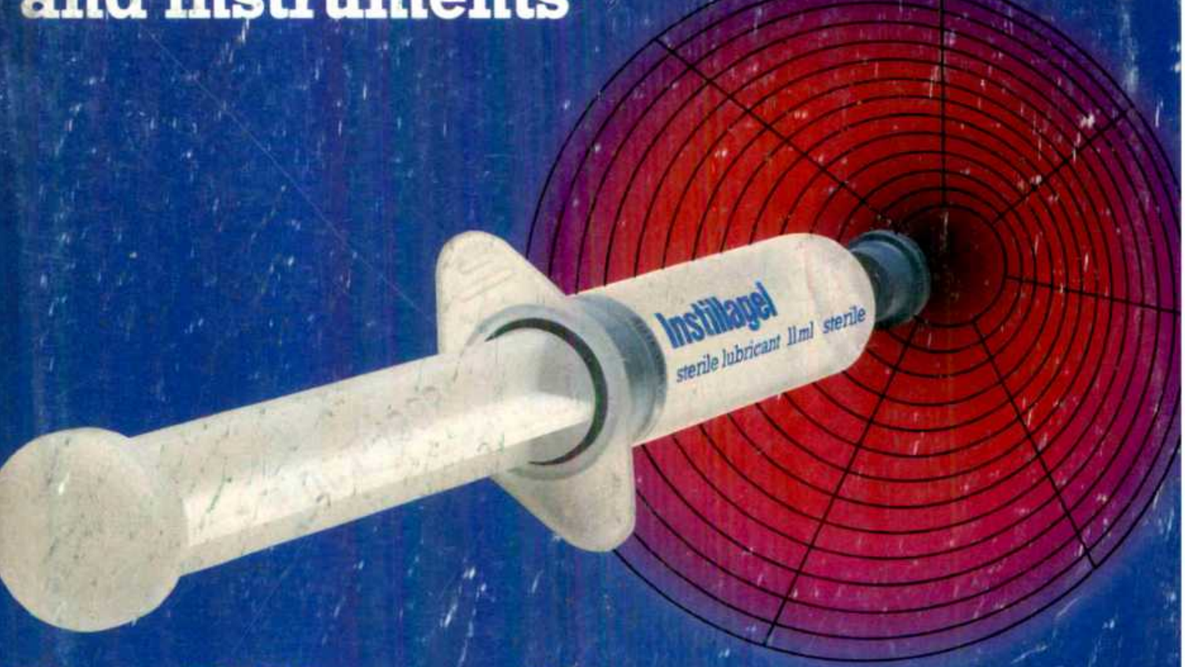

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